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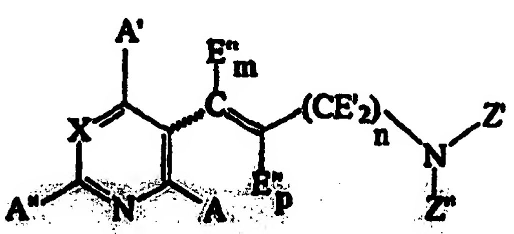

(I)

(a)

(57) Abstract

Patients susceptible to or suffering from central nervous system disorders (e.g., Alzheimer's disease, Parkinson's disease, Tourette's syndrome, attention deficit disorder or schizophrenia) are treated by administering an effective amount of an aryl substituted olefinic amine compound of Formula (I): wherein X is C-R', C-OR', C-CH_2-OR' wherein R' is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino-substituted aromatic group containing species; E' is hydrogen or C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; E'' is C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; Z' and Z'' are each individually selected from the group consisting of hydrogen, C_1-C_5 alkyl, aryl rings, and can form a ring structure (a); A, A' and A'' are each individually selected from the group consisting of hydrogen, C_1-C_7 alkyl, and halo; m is 0 or 1; p is 0 or 1 with the proviso that when m or p is 0 then that E'' is hydrogen; and the wavy line in the structure represents a cis (Z) or trans (E) form of the compound. Exemplary compounds include (E)-N-methyl-4-[3-(benzyloxypyridin)yl]-3-buten-1-amine, (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine, (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine, (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine, and (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine.

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PHARMACEUTICAL COMPOSITIONS INCORPORATING ARYL SUBSTITUTED OLEFINIC AMINE COMPOUNDS

Background of the Invention

The present invention relates to pharmaceutical compositions, and particularly pharmaceutical compositions incorporating compounds which are capable of affecting nicotinic chlorinergic receptors. The present invention also relates to methods for treating a wide variety of conditions and disorders, and particularly conditions and disorders associated with dysfunction of the central and automatic nervous systems.

Nicotine has been proposed to have a number of pharmacological effects. See, for example, Pullan et al. *N. Engl. J. Med.* 330:811-815 (1994). Certain of those effects may be related to effects upon neurotransmitter release. *See for example*, Sjak-shie et al., *Brain Res.* 624:295 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported by Rowell et al., *J. Neurochem.* 43:1593 (1984); Rapier et al., *J. Neurochem.* 50:1123 (1988); Sandor et al., *Brain Res.* 567:313 (1991) and

Vizi, *Br. J. Pharmacol.* **47**:765 (1973). Release of norepinephrine by neurons upon administration of nicotine has been reported by Hall et al., *Biochem. Pharmacol.* **21**:1829 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., *Arch. Int. Pharmacodyn. Ther.* **296**:91 (1977). Release of glutamate by neurons upon administration of nicotine has been reported by Toth et al., *Neurochem Res.* **17**:265 (1992). In addition, nicotine reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used for the treatment of certain CNS disorders. *See*, Sanberg et al., *Pharmacol. Biochem. & Behavior* **46**:303 (1993); Harsing et al., *J. Neurochem.* **59**:48 (1993) and Hughes, *Proceedings from Intl. Symp. Nic.* **S40** (1994). Furthermore, various other beneficial pharmacological effects of nicotine have been proposed. *See*, Decina et al., *Biol. Psychiatry* **28**:502 (1990); Wagner et al., *Pharmacopsychiatry* **21**:301 (1988); Pomerleau et al., *Addictive Behaviors* **9**:265 (1984); Onaivi et al., *Life Sci.* **54(3)**:193 (1994) and Hamon, *Trends in Pharmacol. Res.* **15**:36.

Various nicotinic compounds have been reported as being useful for treating a wide variety of conditions and disorders. See, for example, Williams et al. *DN&P* **7(4)**:205-227 (1994), Arneric et al., *CNS Drug Rev.* **1(1)**:1-26 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* **5(1)**:79-100 (1996), Bencherif et al., *JPET* **279**:1413 (1996), Lippiello et al., *JPET* **279**:1422 (1996), PCT WO 94/08992, PCT WO 96/31475, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., and 5,604,231 to Smith et al. Nicotinic compounds are particularly useful for treating a wide variety of Central Nervous System (CNS) disorders.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose

clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning, orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a neurotransmitter involved in learning and memory mechanisms). *See*, Jones, et al., *Intern. J. Neurosci.* **50**:147 (1990); Perry, *Br. Med. Bull.* **42**:63 (1986); and Sitaram, et al., *Science* **201**:274 (1978). It has been observed that nicotinic acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. *See*, Giacobini, *J. Neurosci. Res.* **27**:548 (1990); and Baron, *Neurology* **36**:1490 (1986). As such, it would seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Certain attempts have been made to treat SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such receptors upon chronic administration to animals. *See*,

Rowell, *Adv. Behav. Biol.* **31**:191 (1987); and Marks, *J. Pharmacol. Exp. Ther.* **226**:817 (1983). It also has been proposed that nicotine can act directly to elicit the release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. *See*, Rowell, et al., *J. Neurochem.* **43**:1593 (1984); Sherwood, *Human Psychopharm.* **8**:155 (1993); Hodges, et al., *Bio. of Nic.* Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., *Br. J. Psych.* **154**:797 (1989); and U.S. Patent Nos. 4,965,074 to Leeson and 5,242,935 to Lippiello et al. Other methods for treating SDAT have been proposed, including U.S. Patent Nos. 5,212,188 to Caldwell et al. and 5,227,391 to Caldwell et al., European Patent Application No. 588,917 and PCT WO 96/30372. Another proposed treatment for SDAT is COGNEX®, which is a capsule containing tacrine hydrochloride, available from Parke-Davis Division of Warner-Lambert Company, which reportedly preserves existing acetylcholine levels in patients treated therewith.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. *See*, Rinne, et al., *Brain Res.* **54**:167 (1991) and Clark, et al., *Br. J. Pharm.* **85**:827 (1985). It also has been proposed that nicotine can ameliorate the symptoms of PD. *See*, Smith et al., *Rev. Neurosci.* **3(1)**:25 (1992).

Certain attempts have been made to treat PD. One proposed treatment for PD is SINEMET CR®, which is a sustained-release tablet containing a mixture of carbidopa and levodopa, available from The DuPont Merck Pharmaceutical Co. Another proposed treatment for PD is ELDEPRYL®, which is a tablet containing selefiline hydrochloride, available from Somerset Pharmaceuticals, Inc. Another proposed treatment for PD is PARLODEL , which is a tablet containing bromocriptine mesylate, available

from Sandoz Pharmaceuticals Corporation. Another method for treating PD and a variety of other neurodegenerative diseases has been proposed in U.S. Patent No. 5,210,076 to Berliner et al.

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of neurological and behavioral symptoms. Typical symptoms include (i) the onset of the disorder before the age of 21 years, (ii) multiple motor and phonic tics although not necessarily concurrently, (iii) variance in the clinical phenomenology of the tics, and (iv) occurrence of quasi daily tics throughout a period of time exceeding a year. Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing; while phonic or vocal tics include throat clearing, sniffling, yelping, tongue clicking and uttering words out of context. The pathophysiology of TS presently is unknown, however it is believed that neurotransmission dysfunction is implicated with the disorder. *See*, Calderon-Gonzalez et al., *Intern. Pediat.* **8(2)**:176 (1993) and OXFORD TEXTBOOK OF MEDICINE, Eds. Weatherall et al., Chapter 21.218 (1987).

It has been proposed that nicotine pharmacology is beneficial in suppressing the symptoms associated with TS. *See*, Devor et al., *The Lancet* **8670**:1046 (1989); Jarvik, *British J. of Addiction* **86**:571 (1991); McConville et al., *Am. J. Psychiatry* **148(6)**:793 (1991); Newhouse et al., *Brit. J. Addic.* **86**:521 (1991); McConville et al., *Biol. Psychiatry* **31**:832 (1992); and Sanberg et al., *Proceedings from Intl. Symp. Nic.* S39 (1994). It also has been proposed to treat TS using HALDOL®, which is haloperidol available from McNeil Pharmaceutical; CATAPRES®, which is clonidine available from Boehringer Ingelheim Pharmaceuticals, Inc., ORAP®, which is pimozide available from Gate Pharmaceuticals; PROLIXIN®, which is fluphenazine available from Apothecon Division of Bristol-Myers Squibb Co.; and KLONOPIN®, which is clonazepam available from Hoffmann-LaRoche Inc.

Attention deficit disorder (ADD) is a disorder which affects mainly children, although ADD can affect adolescents and adults. *See*, Vinson, *Arch. Fam. Med.* **3(5)**:445 (1994); Hechtman, *J. Psychiatry Neurosci.*

19(3):193 (1994); Faraone et al., *Biol. Psychiatry* 35(6):398 (1994) and Malone et al., *J. Child Neurol.* 9(2):181 (1994). Subjects suffering from the disorder typically have difficulty concentrating, listening, learning and completing tasks; and are restless, fidgety, impulsive and easily distracted. Attention deficit disorder with hyperactivity (ADHD) includes the symptoms of ADD as well as a high level of activity (e.g., restlessness and movement). Attempts to treat ADD have involved administration of DEXEDRINE®, which is a sustained release capsule containing dextroamphetamine sulfate, available from SmithKline Beecham Pharmaceuticals; RITALIN®, which is a tablet containing methylphenidate hydrochloride, available from Ciba Pharmaceutical Company; and CYLERT®, which is a tablet containing premoline, available from Abbott Laboratories. In addition, it has been reported that administration of nicotine to an individual improves that individual's selective and sustained attention. *See*, Warburton et al., *Cholinergic Control of Cognitive Resources, Europsychobiology*, Eds. Mendlewicz, et al., pp. 43-46 (1993) and Levin et al. *Psychopharmacology* 123:55-63 (1996).

Schizophrenia is characterized by psychotic symptoms including delusions, catatonic behavior and prominent hallucinations, and ultimately results in a profound decline in the psychosocial affect of the subject suffering therefrom. Traditionally, schizophrenia has been treated with KLONOPIN®, which is available as a tablet containing clonezepam, available from Hoffmann-LaRoche, Inc.; THORAZINE®, which is available as a tablet containing chlorpromazine, available from SmithKline Beecham Pharmaceuticals; and CLORAZIL®, which is a tablet containing clozapine, available from Sandoz Pharmaceuticals. Such neuroleptics are believed to be effective as a result of interaction thereof with the dopaminergic pathways of the CNS. In addition, a dopaminergic dysfunction possessed by individuals suffering from schizophrenia has been proposed. *See*, Lieberman et al., *Schizophr. Bull.* 19:371 (1993) and Glassman, *Amer. J. Psychiatry* 150:546 (1993). Nicotine has been proposed as being effective in effecting neurotransmitter dysfunction associated with schizophrenia. *See*, Merriam et

al., *Psychiatr. Annals* **23**:171 (1993) and Adler et al., *Biol. Psychiatry* **32**:607 (1992). See also Freedman et al., *Proc. Natl. Acad. Sci.* **94**:587-592 (1997).

It would be desirable to provide a useful method for the prevention and treatment of a disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a disorder. It would be highly beneficial to provide individuals suffering from certain disorders (e.g., CNS diseases) with interruption of the symptoms of those disorders by the administration of a pharmaceutical composition containing an active ingredient having nicotinic pharmacology and which has a beneficial effect (e.g., upon the functioning of the CNS), but which does not provide any significant associated side effects (e.g., increased heart rate and blood pressure attendant with interaction of that compound with cardiovascular sites). It would be highly desirable to provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors, such as those which have the potential to affect the functioning of the CNS, but which compound does not significantly affect those receptors which have the potential to induce undesirable side effects (e.g., appreciable pressor cardiovascular effects and appreciable activity at skeletal muscle sites).

Summary of the Invention

The present invention relates to aryl substituted olefinic amine compounds. Such compounmds are useful for providing prevention or treatment of central nervous system (CNS) disorders.

In another aspect, the present invention relates to pharmaceutical compositions comprising effective amounts of compounds of the present invention. The pharmaceutical compositions of the present invention each include a compound which is capable of interacting with nicotinic receptor sites of a patient, and thereby acting as a therapeutic agent in the prevention or treatment of a CNS disorder.

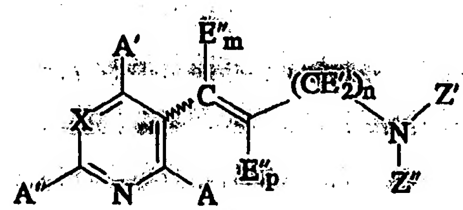
In another aspect, the present invention relates to a method for providing prevention or treatment of central nervous system (CNS) disorders.

In particular, the method involves administering an aryl substituted olefinic amine compound according to the present invention.

The pharmaceutical compositions of the present invention are useful for the prevention and treatment of CNS disorders. The pharmaceutical compositions provide therapeutic benefit to individuals suffering from certain CNS disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions have the potential to (i) exhibit nicotinic pharmacology and affect nicotinic receptors sites in the CNS (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) not provide appreciable adverse side effects (e.g., significant increases in blood pressure and heart rate, and significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of CNS disorders.

Detailed Description of the Invention

The compounds of the present invention include compounds of the formula I:



I

where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, and generally greating than 0.2, and even greater than 0.3; less than 0 and generally less

than -0.1; or 0; as determined in accordance with Hansch et al., *Chem. Rev.* **91**:165 (1991); n is an integer which is 1, 2, 3, 4, 5, 6, 7, or 8, preferably is 1, 2, or 3, and most preferably is 2 or 3; E′ represents hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl) or halo substituted lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as trifluoromethyl or trichloromethyl), but preferably is H; E″ represents lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl) or halo substituted lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as trifluoromethyl or trichloromethyl); Z′ and Z″ individually represent hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl), and preferably at least one of Z′ and Z″ is hydrogen, and most preferably Z′ is hydrogen and Z″ is methyl; alternatively Z′ is hydrogen and Z″ represents a ring structure (cycloalkyl or aromatic), such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, quinuclidinyl, pyridinyl, quinolinyl, pyrimidinyl, phenyl, benzyl (where any of the foregoing can be suitably substiuted with at least one substituent group, such as alkyl, halo, or amino substituents); alternatively Z′, Z″, and the associated nitrogen atom can form a ring structure such as aziridinyl, azetidinyl, pyrollidinyl, piperidinyl, piperazinyl, or morpholinyl; A, A′ and A″ individually represent hydrogen, halo (e.g., F, Cl, Br, or I), alkyl (e.g., lower straight chain or branched C_{1-8} alkyl, but preferably methyl or ethyl), or NX″X‴ where X″ and X‴ are individually hydrogen or lower alkyl, including C_1-C_8, preferably C_1-C_5 alkyl; m is 0 or 1, preferably 0; p is 0 or 1, preferably 0; the wavy line in the structure represents a cis (Z) or trans (E) form of the compound. When m or p is 0, E″ is not present and H fills the valence of the carbon on which E″ is positioned. More specifically, X includes N, C-H, C-F, C-Cl, C-Br, C-I, C-R′, C-NR′R″, C-CF_3, C-OH, C-CN, C-NO_2, C-C_2R′, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR′, C-SR′, C-C(=O)NR′R″, C-NR′C(=O)R′, C-C(=O)R′,

C-C(=O)OR′, C$(CH_2)_q$OR′, C-OC(=O)R′, COC(=O)NR′R″ and C-NR′C(=O)OR′ where R′ and R″ are individually hydrogen or lower alkyl (e.g., C_1-C_{10} alkyl, preferably C_1-C_5 alkyl, and more preferably methyl, ethyl, isopropyl or isobutyl), an aromatic group-containing species or a substituted aromatic group-containing species, and q is an integer from 1 to 6. R′ and R″ can be straight chain or branched alkyl, or R′ and R″ can form a cycloalkyl funtionality (e.g., cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and quinuclidinyl). Representative aromatic group-containing species include pyridinyl, quinolinyl, pyrimidinyl, phenyl, and benzyl (where any of the foregoing can be suitably substituted with at least one substituent group, such as alkyl, halo, or amino substituents). Other representative aromatic ring systems are set forth in Gibson et al., *J. Med. Chem.* 39:4065 (1996). When X represents a carbon atom bonded to a substituent species, that substituent species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In certain circumstances the substituent species is characterized as having a sigma m value not equal to 0. In addition, it is highly preferred that A is hydrogen, it is preferred that A′ is hydrogen, and normally A″ is hydrogen. Generally, both A and A′ are hydrogen; sometimes A and A′ are hydrogen, and A″ is amino, methyl or ethyl; and often A, A′ and A″ are all hydrogen. Depending upon the identity and positioning of each individual E′, certain compounds can be optically active. Typically, the values of each of m and p, and the selection of E′, are such that up to about 4, and frequently up to 3, of the substituents designated as E′ and E″ are non-hydrogen substituents (i.e., substituents such as lower alkyl or halo-substituted lower alkyl).

Of particularly interest are compounds of Formula I where n, m, p, X, A, A′, A″, E′, E″, Z′, and Z″ are as defined hereinbefore, and those compounds can have the cis (Z) or trans (E) form. For such compounds of particular interest, X most preferably is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2, and even greater than 0.3;

less than 0 and generally less than -0.1; or 0. More specifically, the compounds of particular interest are those compounds wherein X is CH, C-Br, $C(CH_2)_qOR'$, where R′ is an aromatic ring, particularly phenyl; C-O-R′ where R′ is an aromatic ring, particularly phenyl; C-O-R′ where R′ is an alkyl particularly isopropyl or ethyl; C-COR′ where R′ is methyl.

One representative compound is (E)-N-methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine for which X is $C\text{-}O\text{-}CH_2Ar$, where Ar is phenyl, E′ is H, n is 2, m is 0, p is 0, A, A′, A″, and Z′ are each H, and Z″ is methyl. Another representative compound is (E)-4-[3-(5-bromopyrdin)yl]-3-buten-1-amine for which X is C-Br, E′ is H, n is 2, m is 0, p is 0, and A, A′, A″, Z′ and Z″ are each H. Another representative compound is (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine for which X is C-O-Ar where Ar is phenyl, E′ is H, n is 2, m is 0, p is 0, A, A′, A″, and Z′ are each H, and Z″ is methyl. Another representative compound is (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine for which X is C-O-R′ where R′ is isopropyl, E′ is H, n is 2, m is 0, p is 0, A, A′, A″, and Z′ are each H, and Z″ is methyl. Another representative compound is (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl-3-buten-1-amine for which X is $C\text{-}CH_2\text{-}O\text{-}CH_3$, E′ is H, n is 2, m is 0, p is 0, A, A′, A″, and Z′ are each H, and Z″ is methyl. Another representative compound is (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine for which X is C-R′ where R′ is phenyl, E′ is H, n is 2, E″ is H, m is 0, p is 0, A, A′, A″, and Z′ are each H, and Z″ is methyl. Another representative compound is (E)-4-(3-pyridinyl)-3-buten-1-amine for which X is CH_2, E′ is H, n is 2, m is 0, p is 0, and A, A′, A″, Z′ and Z″ are each H. Another representative compound is (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine, for which X is C-O-R′ where R′ is ethyl, E′ is H, n is 2, m is 0, p is 0, A, A′, A″, Z′ are each H, and Z″ is methyl.

Another representative compound is (E)-N-methyl-4-[3-5-(ethylthiopyridinyl)]-3-buten-1-amine for which X is $C\text{-}S\text{-}C_2H_5$, E′ is H, n is 2, m is 0, p is 0, and A, A′, A″ and Z′ are each H and Z″ is methyl. Another representative compound is (E)-N-methyl-4-[3-5-acetamidopyridinyl]-3-buten-

1-amine for which X is C-NH-C(=O)-CH_3, E′ is H, n is 2, m is 0, p is 0, and A, A′, A″ and Z′ are each H and Z″ is methyl. Another representative compound is (E)-N-methyl-4-[3-5-carbamoyl-pyridinyl]-3-buten-1-amine for which X is C-C(=O)-NH_2, E′ is H, n is 2, m is 0, p is 0, and A, A′, A″ and Z′ are each H and Z″ is methyl.

The manner in which aryl substituted olefinic amine compounds of the present invention are provided can vary. (E)-metanicotine can be prepared using the techniques set forth by Löffler et al., *Chem. Ber.* **42**:3431 (1909) and Laforge, *J.A.C.S.* **50**:2477 (1928). Certain novel 6-substituted metanicotine-type compounds can be prepared from the corresponding 6-substituted nicotine-type compounds using the general methods of Acheson et al., *J. Chem. Soc., Perkin Trans. 1* **2**:579 (1980). The requisite precursors for such compounds, i.e., 6-substituted nicotine-type compounds, can be synthesized from 6-substituted nicotinic acid esters using the general methods disclosed by Rondahl, *Acta Pharm. Suec.* **14**:113 (1977). Preparation of certain 5-substituted metanicotine-type compounds can be accomplished from the corresponding 5-substituted nicotine-type compounds using the general method taught by Acheson et al., *J. Chem. Soc., Perkin Trans. 1* **2**:579 (1980). The 5-halo nicotine-type compounds and the 5-amino nicotine-type compounds can be prepared using the general procedures disclosed by Rondahl, *Act. Pharm. Suec.* **14**:113 (1977). The 5-trifluoromethyl nicotine-type compounds can be prepared using the techniques and materials set forth in Ashimori et al., *Chem. Pharm. Bull.* **38(9)**:2446 (1990) and Rondahl, *Acta Pharm. Suec.* **14**:113 (1977). Certain metanicotine-type compounds (e.g., 3-(5-phenylpyridin)yl-3-alkene-amine type compounds) can be prepared using the types of synthetic methodologies set forth in Miyaura et al., *Synth. Commun.* **11**:513 (1981) and U.S. Patent No. 5,409,920 to Guthikonda et al. Furthermore, preparation of certain metanicotine-type compounds can be accomplished using a palladium catalyzed coupling reaction of an aromatic halide and a terminal olefin containing a protected amine substituent, removal of the protective group to obtain a primary amine, and optional alkylation to

provide a secondary or tertiary amine. In particular, certain metanicotine-type compounds can be prepared by subjecting a 3-halo substituted, 5-substituted pyridine compound or a 5-halo substituted pyrimidine compound to a palladium catalyzed coupling reaction using an olefin possessing a protected amine functionality (e.g., an olefin provided by the reaction of a phthalimide salt with 3-halo-1-propene, 4-halo-1-butene, 5-halo-1-pentene or 6-halo-1-hexene). *See*, Frank et al., *J. Org. Chem.* 43(15):2947 (1978) and Malek et al., *J. Org. Chem.* 47:5395 (1982). Alternatively, certain metanicotine-type compounds can be prepared by coupling an N-protected, modified amino acid residue, such as 4-(N-methyl-N-tert-butyloxycarbonyl)amino-butyric acid methyl ester, with an aryl lithium compound, as can be derived from a suitable aryl halide and butyl lithium. The resulting N-protected aryl ketone is then chemically reduced to the corresponding alcohol, converted to the alkyl halide, and subsequently dehydrohalogenated to introduce the olefin functionality. Removal of the N-protecting group affords the desired metanicotine-type compound.

There are a number of different methods for providing (Z)-metanicotine-type compounds. In one method, (Z)-metanicotine-type compounds can be synthesized from nicotine as a mixture of the E and Z isomers; and the (Z)-metanicotine-type compounds can then be separated by chromatography using the types of techniques disclosed by Sprouse et al., Abstracts of Papers, p. 32, Coresta/TCRC Joint Conference (1972). In another method, (Z)-metanicotine can be prepared by the controlled hydrogenation of the corresponding acetylenic compound (e.g., N-methyl-4-(3-pyridinyl)-3-butynylamine). For example, certain 5-substituted (Z)-metanicotine-type compounds and certain 6-substituted (Z)-metanicotine-type compounds can be prepared from 5-substituted-3-pyridinecarboxaldehydes and 6-substituted-3-pyridinecarboxaldehydes, respectively.

Representative compounds of the present invention, representative starting materials, and methods of synthesizing representative compounds and suitable salts thereof are set forth in U.S. Patent Nos.

5,597,919 to Dull et al.; U.S. Patent Application Serial No. 08/631,762; U.S. Patent Application Serial No. 08/635,165; and PCT No. WO 96/31475.

One representative compound, (E)-N-methyl-4-(3-[5-(ethylthio)pyridinyl])-3-buten-1-amine is prepared from N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine and 3-bromo-5-(ethylthio)pyridine using the techniques set forth in W.C. Frank, et al., *J. Org. Chem.* 43(15):2947 (1978), and the tert-butoxy carbonyl protecting group is subsequently removed. Specifically, N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine is prepared by (i) reacting 4-bromo-1-butene at 0.035 mole scale with a ten fold excess of condensed methylamine in N,N-dimethylformamide solvent in the presence of potassium carbonate to provide a 97% yield of N-mehtyl-3-buten-1-amine; (ii) the amine thus prepared is reacted at 0.030 mole scale with one equivalent of di-tert-butyldicarbonate in tetrahydrofuran to give N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine in 68% yield. The 3-bromo-5-(ethylthio)pyridine is produced by the reaction of sodium ethanethiolate on 3,5-dibromopyridine in N,N-dimethylformamide in 86% yield. N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine and 3-bromo-5-(ethylthio)pyridine are reacted using the Heck reaction on a 1.6 mmole scale in 2:1 acetonitrile:triethylamine using a catalyst consistingof one mole percent palladium acetate and four mole percent tri-o-tolylphosphine. N-methyl-N-(tert-butoxycarbonyl)-4-(3-[5-(ethylthio)pyridinyl])-3-buten-1-amine is obtained in 59% yield. Deprotection of the product may then be accomplished by 1:1 6N hydrochloric acid:tetrahdyrofuran.

Other representative compounds include (E)-N-methyl-4-[3-(5-acetamidopyridinyl)]-3-buten-1-amine and (E)-N-methyl-4-[3-(5-carbamoylpyridinyl)]-3-buten-1-amine. These compounds may be produced according to the techniques set forth in C.V. Greco et al., *J. Heterocyclic Chem.* 7(4):761 (1970). More specifically, the commercially available starting material, 5-bromonicotinic acid is converted to both 5-bromonicotinamide and 3-amino-5-bromopyridine. The 3-amino-5-bromopyridine can be acylated with acetic anhydride to give 3-acetamido-5-bromopyridine. 3-Acetamido-5-

bromopyridine may then be reacted with N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine (prepared according to the preceeding techniques) using the Heck reaction described hereinabove and set forth in W.C. Frank et al., *J. Org. Chem.* 43(15):2947 (1978). The reaction gives (E)-N-methyl-N-(tert-butoxycarbonyl)-4-[3-(5-acetamidopyridinyl)]-3-buten-1-amine. The Heck reaction of 5-bromonicotinic acid with N-methyl-N-(tert-butoxycarbonyl)-3-buten-1-amine gives (E)-N-methyl-N-(tert-butoxycarbonyl)-4-[3-(5-carbamoylpyridinyl)]-3-buten-1-amine. The treatment of either product with aqueous acid effects the removal of the tert-butoxycarbonyl groups from these compounds, giving the 5-acetamido and 5-carbamoyl substituted metanicotinic compounds respectively.

The present invention relates to a method for providing prevention of a CNS disorder to a subject susceptible to such a disorder, and for providing treatment to a subject suffering from a CNS disorder. In particular, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of the CNS disorder (i.e., provide protective effects), amelioration of the symptoms of the CNS disorder, and amelioration of the reoccurrence of the CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. The compounds normally are not optically active. However, certain compounds can possess substituent groups of a character so that those compounds possess optical activity. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate,

fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

CNS disorders which can be treated in accordance with the present invention include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, anticoagulants, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics, steroids and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular CNS disorder.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al.); topically (e.g., in lotion form); orally

(e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); or transdermally (e.g., using a transdermal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Ciba-Geigy Corporation and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, such as a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that effect the functioning of the CNS.

The dose of the compound is that amount effective to prevent occurrence of the symptoms of the condition being prevented, or to treat some symptoms of the condition from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant an amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the CNS disorder. Thus, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to elicit neuropharmacological effects (e.g., elicit neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by a prolonging or

delaying of the onset of the symptoms of the condition. Treatment of the condition is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms experienced by the patient, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than -0.5, often are greater than about 0, and frequently are greater than about 0.5. The log P values of such typical compounds generally are less than about 3.5, often are less than about 3.0, and frequently are less than about 2.5. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. *See*, Hansch, et al., *J. Med. Chem.* 11:1 (1968).

The compounds useful according to the method of the present invention have the ability to interact with certain nicotinic cholinergic receptors in the brain of the patient. As such these compound have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in

carrying out the present invention generally exceed about 1 nM, often exceed about 5 nM, and frequently exceed about 10 nM. The receptor binding constants of such typical compounds generally are less than about 1000 nM, often are less than about 500 nM, frequently are less than about 200 nM, and even less than 100 nM. Receptor binding constants provide a measure of the ability of the compound to bind to relevant receptor sites of certain cells of the patient. *See*, Cheng, et al., *Biochem. Pharmacol.* **22**:3099 (1973).

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic pharmacology by effectively eliciting neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, these compounds have the ability to cause relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, the compounds useful in carrying out the present invention provide for the secretion of dopamine in amounts of at least about 10 percent, often at least about 25 percent, frequently at least about 50 percent and even greater than 75 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine. Certain compounds of the present invention can provide secretion of dopamine in an amount which can exceed that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from muscle preparations. Thus, such compounds exhibit receptor activation constants or EC50 values (i.e., which provide a measure of the concentration of compound needed to activate half of the relevant receptor sites of the skeletal muscle of a patient) which are relatively high. Generally, typical compounds useful in carrying out the present invention activate isotopic rubidium ion flux by less than 20 percent,

often by less than 15 percent, and frequently by less than 10 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue. As such, the compounds of the present invention have poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, the compounds useful in the present invention activate isotopic rubidium ion flux by less than 25 percent, often by less than 15 percent, frequently by less than 10 percent, and even essentially 0 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of CNS disorders amelioration of the symptoms of such disorders, and amelioration to some degree of the reoccurrence of such disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as demonstrated by increased effects relating to the cardiovascular system, and effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration

of a compound of the present invention resulting in treatment of a CNS disorder occurs upon administration of less than 1/5, often less than 1/10, and frequently less than 1/15, that amount sufficient to cause any side effects to a significant degree.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted.

EXAMPLE 1

Sample No. 1 is (E)-N-Methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine, which was prepared according to the following procedure.

3-Bromo-5-benzyloxypyridine: Under a nitrogen atmosphere, small pieces of sodium (1.48 g, 64.4 mmol) were added to benzyl alcohol (17.11 g, 158.0 mmol), and the mixture was stirred and heated at 70°C for 18 h. To the stirring, viscous mixture was added 3,5-dibromopyridine (5.00 g, 21.1 mmol), copper powder (255 mg, 4.0 mmol), and benzyl alcohol (15 mL). The mixture was further heated at 100°C for 48 h. The reaction mixture was allowed to cool to ambient temperature, diluted with water (50 mL), and extracted with diethyl ether (5 x 50 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. Vacuum distillation removed excess benzyl alcohol, bp 68-72°C at 2.6 mm Hg. Further vacuum distillation afforded 3.17 g (38.0%) of 3-bromo-5-benzyloxypyridine as a white, crystalline solid, mp 64-66°C.

^1H NMR ($CDCl_3$, 300 MHz): δ 8.28 (2H, m), 7.42-7.34 (6H, m), 5.08 (2H, s).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.20, 143.21, 136.71, 135.44, 128.79, 128.55, 127.55, 126.97, 124.37, 70.65.

HRMS: Calcd. for $C_{12}H_{10}BrNO$ (M^+): m/z 262.994575. Found: 262.995321.

(E)-4-[3-(5-Benzyloxypyridin)yl]-3-buten-1-ol: Under a nitrogen atmosphere, a mixture of 3-buten-1-ol (151 mg, 2.1 mmol), 3-bromo-

5-benzyloxypyridine (528 mg, 2.0 mmol), palladium(II) acetate (5 mg, 0.02 mmol), tri-o-tolylphosphine (25 mg, 0.08 mmol), triethylamine (0.5 mL), and acetonitrile (1.0 mL) was stirred and heated under reflux for 20 h. Upon cooling, the mixture was diluted with water (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined dichloromethane extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give a dark-yellow oil (527 mg). Purification by column chromatography on silica gel, eluting with 2.5% (v/v) methanol in ethyl acetate afforded 387 mg (75.8%) of (E)-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-ol as a colorless gum.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (1H, d, J = 2.7 Hz), 8.18 (1H, d, J = 1.6 Hz), 7.41-7.33 (5H, m), 7.25 (1H, s), 6.44 (1H, d, J = 15.9 Hz), 6.27 (1H, dt, J = 16.0, 7.0 Hz), 5.09 (2H, s), 3.77 (2H, t, J = 6.2 Hz), 2.44 (2H, dq, J = 6.2, 1.0 Hz), 1.67 (1H, br s).

<u>(E)-N-Methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine:</u> Under a nitrogen atmosphere, a cold (0°C), stirring solution of (E)-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-ol (368 mg, 1.44 mmol), dichloromethane (1.5 mL), and pyridine (1 drop) was treated with p-toluenesulfonyl chloride (302 mg, 1.58 mmol). The mixture was allowed to warm to ambient temperature. After stirring for 16 h, the solution was concentrated under a stream of nitrogen, and the residue was further dried under high vacuum. The resulting residue was dissolved in tetrahydrofuran (3 mL), and 40% aqueous methylamine (3 mL) was added. The solution was stirred 6 h at ambient temperature and was then concentrated by rotary evaporation to a dark gum. The residue was partitioned between 1 M NaOH solution (10 mL) and chloroform (10 mL). The chloroform layer was separated, washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give a dark-brown oil (445 mg). The product was purified by column chromatography on silica gel, eluting with 2.5% (v/v) triethylamine in methanol to give 162 mg (41.9%) of (E)-N-methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine as a light-yellow oil.

^1H NMR ($CDCl_3$, 300 MHz): δ 8.20 (1H, d, J = 2.7 Hz), 8.17 (1H, d, J = 1.8 Hz), 7.43-7.33 (5H, m), 7.22 (1H, m), 6.40 (1H, d, J = 15.9 Hz), 6.24 (1H, dt, J = 15.9, 6.9 Hz), 5.09 (2H, s), 2.72 (2H, t, J = 6.8 Hz), 2.46-2.39 (2H, m), 2.44 (3H, s), 1.76 (1H, br s).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.92, 140.88, 136.73, 136.17, 133.70, 131.03, 128.71, 128.29, 127.91, 127.53, 117.93, 70.32, 51.03, 36.29, 33.47.

HRMS: Calcd. for $C_{17}H_{20}N_2O$ (M^+): m/z 268.157563. Found: 268.157420.

EXAMPLE 2

Sample No. 2 is (E)-4-[3-(5-Bromopyridin)yl]-3-buten-1-amine Hemifumarate, which was prepared according to the following techniques.

N-3-Buten-1-phthalimide was prepared essentially in accordance with the techniques described in W. C. Frank, et al., *J. Org. Chem.* **43**:2947 (1978).

(E)-N-4-[3-(5-Bromopyridin)yl]-3-buten-1-phthalimide: Under a nitrogen atmosphere, a mixture of N-3-buten-1-phthalimide (8.74 g, 43.5 mmol), 3,5-dibromopyridine (10.00 g, 42.2 mmol), palladium(II) acetate (190 mg, 0.84 mmol), tri-o-tolylphosphine (514 mg, 1.69 mmol), and triethylamine (8.55 g, 84.4 mmol) was stirred at 100-107°C (oil bath temperature) for 48 h. Upon cooling to ambient temperature, the brown residue was filtered, washed with water (200 mL), and dissolved in hot N,N-dimethylformamide (45 mL). The resulting solution was filtered through Celite® filter aid. Water (50 mL) was added to the filtrate, and the mixture was cooled at 5°C for 18 h. The resulting solids were filtered, washed with cold water, followed by cold 2-propanol (10 mL), and vacuum dried at 50°C to give a yellowish brown semisolid (13.69 g). The product was recrystallized twice from toluene (40 mL), filtered, washed with cold toluene (5 mL) and cold 2-propanol (5 mL), and vacuum dried at 50°C to give 2.11 g (14.0%) of (E)-N-4-[3-(5-

bromopyridin)yl]-3-buten-1-phthalimide as a light beige powder, mp 145-148°C.

^{1}H NMR ($CDCl_3$): δ 8.46 (1H, d, J = 2.0 Hz), 8.37 (1H, d, J = 1.8 Hz), 7.82 (2H, m), 7.74 (1H, t, J = 2.0 Hz), 7.69 (2H, m), 6.33 (2H, d, J = 15.9 Hz), 6.25 (1H, dt, J = 15.9, 5.9 Hz), 3.84 (2H, t, J = 6.9 Hz), 2.62 (2H, m).

<u>(E)-4-[3-(5-Bromopyridin)yl]-3-buten-1-amine:</u> Under a nitrogen atmosphere, a solution of (E)-N-4-[3-(5-bromopyridin)yl]-3-buten-1-phthalimide (2.16 g, 6.1 mmol), hydrazine hydrate (0.91 g, 18.2 mmol), methanol (40 mL) and chloroform (80 mL) was allowed to stir for 5 h at ambient temperature. The reaction was monitored by thin layer chromatography on silica gel (chloroform-methanol (99:1, v/v)). Additional hydrazine hydrate (0.45 g, 9.1 mmol) was added to the reaction mixture which was stirred at ambient temperature for a total of 45 h. The thick mixture was poured into 1M NaOH solution (750 mL), stirred 30 min at ambient temperature, and extracted with chloroform (3 x 100, 2 x 200 mL). The combined chloroform extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. Further drying under vacuum at ambient temperature afforded a golden oil (1.11 g). Purification by vacuum distillation produced 0.57 g of a light-yellow oil, bp 109°C at 0.05 mm Hg. Further purification by vacuum distillation afforded 180 mg (13.1%) of (E)-4-[3-(5-bromopyridin)yl]-3-buten-1-amine as a light-yellow oil, bp 108-115°C at 0.03 mm Hg.

^{1}H NMR (CD_3OD): δ 8.49 (1H, d, J = 1.8 Hz), 8.45 (1H, d, J = 2.2 Hz), 8.09 (1H, t, J = 2.1 Hz), 6.48 (2H, m), 2.82 (2H, t, J = 7.0 Hz), 2.43 (2H, m). EI-MS: m/z (relative intensity), 227 (M^{+}, 0.1%).

<u>(E)-4-[3-(5-Bromopyridin)yl]-3-buten-1-amine Hemifumarate:</u> (E)-4-[3-(5-Bromopyridin)yl]-3-buten-1-amine (173 mg, 0.76 mmol) in a small volume of 2-propanol, was added to a warm solution of fumaric acid (95.6 mg, 0.82 mmol) in 2-propanol. The white mixture was concentrated by rotary evaporation, and the solids were recrystallized from 2-propanol. The mixture was kept at 5°C for 18 h. The resulting solids were filtered, washed with cold

2-propanol, cold diethyl ether, and dried under vacuum at 50°C to yield a light-beige powder. A second recrystallization from 2-propanol afforded 103 mg (47.4% yield) of (E)-4-[3-(5-bromopyridin)yl]-3-buten-1-amine hemifumarate as a cream-colored powder, mp 175-176.5°C.

^{1}H NMR (D_2O, 300 MHz): δ 8.51 (1H, s), 8.47 (1H, s), 8.12 (1H, s), 6.59 (1H, d, J = 16.0 Hz), 6.51 (1H, s), 6.39 (1H, dt, J = 16.0, 7.0 Hz), 3.20 (2H, t, J = 7.0 Hz), 2.65 (2H, q, J = 7.0 Hz).

^{13}C NMR (D_2O, 75 MHz): δ 174.62, 148.36, 145.32, 136.50, 135.32, 134.73, 129.24, 128.42, 120.64, 38.67, 30.30.

Analysis calculated for $C_9H_{11}BrN_2 \cdot 0.5\ C_4H_4O_4$: C, 46.33; H, 4.59; Br, 28.03; N, 9.83. Found: C, 46.20; H, 4.71; Br, 27.92; N, 9.75.

EXAMPLE 3

Sample No. 3 is (E)-N-Methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine, which was prepared according to the following techniques.

3-Bromo-5-phenoxypyridine: Sodium phenoxide trihydrate (7.50 g, 44.1 mmol) was dried under vacuum at 65°C for 18 h at 0.6 mm Hg to yield 5.08 g of sodium phenoxide. Under a nitrogen atmosphere, 3,5-dibromopyridine (4.00 g, 16.9 mmol) and anhydrous N,N-dimethylformamide (40 mL) were added to the sodium phenoxide (5.08 g, 43.8 mmol). The resulting mixture was stirred at 110°C for 44 h. After cooling to ambient temperature, water (75 mL) was added, and the pH was adjusted to 13.0 using 30% NaOH solution. The solution was extracted with diethyl ether (4 x 60 mL). The combined ether extracts were washed with saturated NaCl solution (50 mL), dried ($NaSO_4$), filtered and concentrated by rotary evaporation to a brown oil (4.0 g). The oil was vacuum distilled, collecting a forerun (317 mg), bp 48-65°C at 0.05 mm Hg. Further distillation afforded 3.35 g (79.8%) of 3-bromo-5-phenoxypyridine as a pale-yellow oil, bp 75-112°C at 0.05 mm Hg (lit. bp 110-115°C at 1.7 mm Hg, *see* K. Fujikawa, et al. *Agr. Biol. Chem.* 34:68 (1970).

^1H NMR ($CDCl_3$, 300 MHz): δ 8.39 (1H, d, J = 1.7 Hz), 8.31 (1H, d, J = 2.3 Hz), 7.42-7.35 (3H, m), 7.22-7.17 (1H, m), 7.05-7.01 (2H, m).

<u>(E)-4-[3-(5-Phenoxypyridin)yl]-3-buten-1-ol:</u> Under a nitrogen atmosphere, a mixture of 3-bromo-5-phenoxypyridine (1.80 g, 7.23 mmol), palladium(II) acetate (15 mg, 0.067 mmol), tri-o-tolylphosphine (80.9 mg, 0.266 mmol), 3-buten-1-ol (494 mg, 6.85 mmol), triethylamine (2.5 mL), and acetonitrile (5 mL) was stirred and heated under reflux for 22 h. The reaction was monitored by thin layer chromatography on silica gel eluting with chloroform-methanol (98:2, v/v). Additional palladium(II) acetate (7.5 mg) and tri-o-tolylphosphine (44 mg) were added to the reaction mixture, which was stirred and heated under reflux for an additional 2 h. After cooling to ambient temperature, the mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with water (25 mL), dried ($NaSO_4$), filtered, and concentrated to yield a dark-yellow oil (1.85 g). The product was purified by column chromatography on silica gel, eluting with chloroform-methanol (94:6, v/v). Selected fractions were combined and concentrated. Purification by vacuum distillation gave 0.468 g of (E)-4-[3-(5-phenoxypyridin)yl]-3-buten-1-ol as a viscous, yellow oil, bp 155-175°C at 0.15 mm Hg. Further distillation produced an additional 1.270 g of product as a viscous, yellow oil, bp 165-175°C at 0.15 mm Hg, for a total yield of 1.738 g (100%).

^1H NMR (CD_2Cl_2, 300 MHz): δ 8.31 (1H, d, J = 1.5 Hz), 8.20 (1H, d, J = 2.4 Hz), 7.41-7.34 (2H, m), 7.29 (1H, t, J = 2.2 Hz), 7.17 (1H, m), 7.04 (2H, m), 6.45 (1H, d, J = 16.0 Hz), 6.27 (1H, dt, J = 15.9, 7.0 Hz), 3.72 (2H, t, J = 6.3 Hz), 2.46 (2H, m), 1.58 (1H, br s).

<u>(E)-N-Methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine:</u> Under a nitrogen atmosphere, methanesulfonyl chloride (0.66 g, 5.8 mmol) was added dropwise to a stirring, ice-cold solution of (E)-4-[3-(5-phenoxypyridin)yl]-3-buten-1-ol (1.27 g, 5.3 mmol), triethylamine (1.07 g, 10.5 mmol), and tetrahydrofuran (15 mL). The mixture was stirred for 48 h at ambient temperature. The dark-brown mixture was diluted with water (50 mL)

and extracted with chloroform (3 x 50 mL). The combined chloroform extracts were dried (Na_2SO_4), filtered, and concentrated to a gold oil (0.873 g). Aqueous methylamine (20 mL, 40% solution) was added to the oil, and the mixture was allowed to stir at ambient temperature for 18 h. The solution was basified with 30% NaOH solution to pH 11-12 and extracted with diethyl ether (4 x 25 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated to a yellow syrup. To purify the product, water (50 mL) was added to the residue, and the pH was adjusted to ~8.0 with 30% HCl solution. The resulting solution was extracted with dichloromethane (50 mL). The aqueous layer was separated, the pH was adjusted to 12.5 using 30% NaOH solution, and this alkaline solution was extracted with tert-butyl methyl ether (3 x 25 mL). Thin layer chromatography analysis on silica gel, eluting with methanol-ammonium hydroxide (10:1, v/v) indicated that the spent dichloromethane layer contained some product. Therefore, water (25 mL) was added to the dichloromethane extract, and the pH was adjusted to 8.0. The aqueous phase was separated, the pH was adjusted to pH 12.5 using 30% NaOH solution, and this solution was extracted with tert-butyl methyl ether (2 x 25 mL). All tert-butyl methyl ether layers were combined, dried ($NaSO_4$), filtered, and concentrated to yield 106.5 mg (8.0%) of (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine as a dark-gold oil.

^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.30 (1H, d, J = 1.8 Hz), 8.18 (1H, d, J = 2.7 Hz), 7.38 (2H, m), 7.28 (1H, t, J = 2.2 Hz), 7.16 (1H, m), 7.06-7.02 (2H, m), 6.41 (1H, d, J = 16.0 Hz), 6.27 (1H, dt, J = 16.0, 6.7 Hz), 2.69 (1H, t, J = 6.8 Hz), 2.40 (3H, s), 2.42-2.35 (2H, m), 1.60 (1H, br s).

^{13}C NMR (CD_2Cl_2, 75 MHz): δ 156.96, 154.27, 143.19, 140.14, 134.59, 131.77, 130.39, 127.86, 124.36, 122.09, 119.30, 51.03, 35.85, 33.20.

HRMS: Calcd. for $C_{16}H_{18}N_2O$ (M^+): m/z 254.141913. Found: 254.142750.

EXAMPLE 4

Sample No. 4 is (E)-N-Methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine, which is prepared according to the following procedure.

3-Bromo-5-isopropoxypyridine: Under a nitrogen atmosphere, 2-propanol (30 mL) was added to potassium (2.4 g, 61.4 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. To the resulting solution was added 3,5-dibromopyridine (4.74 g, 20.0 mmol) and copper powder (250 mg, 3.9 mmol). The mixture was heated under reflux under a nitrogen atmosphere for 70 h. Upon cooling to ambient temperature, the mixture was concentrated under high vacuum to a solid, which was diluted with water (200 mL) and extracted with diethyl ether (3 x 150 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to a dark-brown oil (3.71 g). Purification by column chromatography on silica gel, eluting with 10→20% (v/v) diethyl ether in benzene afforded 1.38 g (31.9%) of 3-bromo-5-isopropoxypyridine as a volatile, colorless oil.

^1H NMR ($CDCl_3$, 300 MHz): δ 8.23 (1H, s), 8.19 (1H, s), 7.31 (1H, t, J = 2.1 Hz), 4.54 (1H, septet, J = 6.0 Hz), 1.34 (6H, d, J = 6.0 Hz).

(E)-4-[3-(5-Isopropoxypyridin)yl]-3-buten-1-ol: Under a nitrogen atmosphere, a mixture of 3-buten-1-ol (296 mg, 4.1 mmol), 3-bromo-5-isopropoxypyridine (864 mg, 4.0 mmol), palladium(II) acetate (9.0 mg, 0.04 mmol), tri-o-tolylphosphine (50.0 mg, 0.16 mmol), triethylamine (1.0 mL), and acetonitrile (2.0 mL) was stirred and heated under reflux for 27 h. Upon cooling to ambient temperature, the mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined dichloromethane extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give an orange oil (843 mg). Purification by column chromatography on silica gel, eluting with 0→4% (v/v) methanol in ethyl acetate afforded 498 mg (60.1%) of (E)-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-ol as a thick, light-yellow oil.

^1H NMR ($CDCl_3$, 300 MHz): δ 8.13 (1H, d, J = 1.4 Hz), 8.10 (1H, d, J = 2.6 Hz), 7.14 (1H, t, J = 2.3 Hz), 6.43 (1H, d, J = 16.0 Hz), 6.26

(1H, dt, J = 15.9, 7.0 Hz), 4.57 (1H, septet, J = 6.0 Hz), 3.76 (2H, t, J = 6.2 Hz), 2.49 (2H, dq, J = 6.1, 1.2 Hz), 1.66 (1H, br s), 1.33 (6H, d, J = 5.9 Hz).

<u>(E)-N-Methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine:</u>

Under a nitrogen atmosphere, a cold (0°C), stirring solution of (E)-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-ol (466 mg, 2.25 mmol), anhydrous dichloromethane (2 mL), and pyridine (2 drops) was treated with p-toluenesulfonyl chloride (540 mg, 2.83 mmol). The mixture was allowed to warm to ambient temperature. After stirring 16 h, the solution was concentrated under a stream of nitrogen, and the residue was further dried under high vacuum. The residue was dissolved in N,N-dimethylformamide (5 mL), and a solution of 2N methylamine in tetrahydrofuran (5 mL) was added. After stirring under a nitrogen atmosphere for 24 h at ambient temperature, the solution was diluted with water (25 mL) and extracted with diethyl ether (2 x 30 mL). The combined ether extracts were washed with water (10 mL) and saturated NaCl solution (20 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to a residue (470 mg). Purification by column chromatography on silica gel, eluting with 2.5% (v/v) triethylamine in absolute ethanol afforded 153 mg (30.9%) of (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine as a reddish, amber oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (1H, d, J = 1.7 Hz), 8.10 (1H, d, J = 2.7 Hz), 7.13 (1H, t, J = 2.1 Hz), 6.40 (1H, d, J = 16.0 Hz), 6.23 (1H, dt, J = 15.9, 6.9 Hz), 4.57 (1H, septet, J = 6.1 Hz), 2.73 (2H, t, J = 6.9 Hz), 2.46-2.40 (2H, m), 2.45 (3H, s), 2.19 (1H, br s), 1.33 (6H, d, J = 6.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.09, 140.41, 137.77, 133.67, 130.56, 128.17, 119.05, 70.62, 50.90, 36.06, 33.26, 21.94.

HRMS: Calcd. for $C_{13}H_{20}N_2O$ (M^+): m/z 220.157563. Found: 220.157686.

EXAMPLE 5

Sample No. 5 is (E)-N-Methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine, which is prepared according to the following procedure.

3-Bromo-5-methoxymethylpyridine: Under a nitrogen atmosphere, a solution of 5-bromonicotinic acid (5.05 g, 25.0 mmol) and thionyl chloride (10 mL) was stirred and heated. The excess thionyl chloride was removed by distillation, and the residue was dried briefly under high vacuum. To the resulting light-yellow solid in dry tetrahydrofuran (40 mL) was added sodium borohydride (1.90 g, 50.0 mmol) at 0°C under a nitrogen atmosphere. The mixture was stirred 1 h at 0°C and allowed to warm to ambient temperature. The mixture was added to a cold, saturated aqueous NH_4Cl solution (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to a semisolid (2.77 g). Thin layer chromatography analysis on silica gel indicated mostly 5-bromonicotinic acid; therefore the semisolid was partitioned between ether and saturated aqueous $NaHCO_3$ solution. The ether layer was separated and concentrated by rotary evaporation to a residue (0.75 g). Purification by column chromatography on silica gel, eluting with ethyl acetate-hexane (1:1, v/v) afforded 379 mg (8.1%) of 3-bromo-5-hydroxymethylpyridine.

Under a nitrogen atmosphere, a solution of 3-bromo-5-hydroxymethylpyridine (379 mg, 2.0 mmol) in dry tetrahydrofuran (10 mL) was treated at ambient temperature with sodium hydride (160 mg, 4.0 mmol, 60% dispersion in mineral oil). After stirring 5 min at ambient temperature, the opaque, yellow mixture was treated with methyl iodide (342 mg, 2.4 mmol). After stirring 2 h at ambient temperature, the mixture was added to cold water (30 mL) and extracted with diethyl ether (3 x 20 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to an orange oil (429 mg). Purification by column chromatography on silica gel, eluting with 15% (v/v) ethyl acetate in hexane

afforded 266 mg (65.3%) of 3-bromo-5-methoxymethylpyridine as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.59 (1H, d, J = 2.0 Hz), 8.45 (1H, s), 7.83 (1H, m), 4.43 (2H, s), 3.40 (3H, s).

<u>(E)-4-[3-(5-Methoxymethylpyridin)yl]-3-buten-1-ol:</u> Under a nitrogen atmosphere, a mixture of 3-buten-1-ol (108 mg, 1.5 mmol), 3-bromo-5-methoxymethylpyridine (240 mg, 1.2 mmol), palladium(II) acetate (5.0 mg, 0.02 mmol), tri-o-tolylphosphine (25.0 mg, 0.08 mmol), triethylamine (0.5 mL), and acetonitrile (1.0 mL) was stirred and heated under reflux for 21 h. Upon cooling to ambient temperature, the mixture was diluted with water (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined dichloromethane extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to an oil (240 mg). Purification by column chromatography on silica gel, eluting with 0→4% (v/v) methanol in ethyl acetate afforded 148 mg (64.5%) of (E)-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-ol as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47 (1H, d, J = 1.8 Hz), 8.37 (1H, d, J = 1.6 Hz), 7.66 (1H, t, J = 2.1 Hz), 6.47 (1H, d, J = 16.0 Hz), 6.32 (1H, dt, J = 16.0, 6.9 Hz), 4.44 (2H, s), 3.77 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 2.50 (2H, dq, J = 6.3, 1.2 Hz), 1.66 (1H, br s).

<u>(E)-N-Methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine:</u> Under a nitrogen atmosphere, a cold (0°C), stirring solution of (E)-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-ol (140 mg, 0.72 mmol), anhydrous dichloromethane (1 mL), and pyridine (1 drop) was treated with p-toluenesulfonyl chloride (172 mg, 0.90 mmol). The mixture was allowed to warm to ambient temperature. After stirring 12 h, the solution was concentrated under a stream of nitrogen, and the residue was further dried under high vacuum. The residue was dissolved in N,N-dimethylformamide (2 mL) and treated with 40% aqueous methylamine solution (1 mL) at 0°C. After stirring under a nitrogen atmosphere for 7 h at ambient temperature, the solution was added to 1M NaOH solution (10 mL) and extracted with diethyl ether (2 x 10 mL). The combined ether extracts were dried (Na_2SO_4), filtered,

and concentrated by rotary evaporation to a residue (99 mg). Purification by column chromatography on silica gel, eluting with 2.5% (v/v) triethylamine in methanol afforded 24 mg (16.1%) of (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine as a light-yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47 (1H, d, J = 2.1 Hz), 8.37 (1H, d, J = 1.9 Hz), 7.65 (1H, t, J = 2.0 Hz), 6.43 (1H, d, J = 16.0 Hz), 6.29 (1H, dt, J = 16.0, 6.7 Hz), 4.44 (2H, s), 3.39 (3H, s), 2.73 (2H, t, J = 6.9 Hz), 2.45 (3H, s), 2.43 (2H, m), 1.56 (1H, br s).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.54, 147.50, 133.29, 132.88, 131.82, 131.08, 127.88, 72.08, 58.39, 51.14, 36.36, 33.56.

HRMS: Calcd. for $C_{12}H_{18}N_2O$ (M^+): m/z 206.141913. Found: 206.142612.

EXAMPLE 6

Sample No. 6 is (E)-4-(3-pyridinyl)-3-buten-1-amine difumarate, which is prepared according to the following techniques.

(E)-4-(3-Pyridinyl)-3-buten-1-amine: This compound was prepared essentially in accordance with the techniques described in W. Frank, et al., *J. Org. Chem.* 43:2947 (1978).

(E)-4-(3-Pyridinyl)-3-buten-1-amine Difumarate:

(E)-4-(3-pyridinyl)-3-buten-1-amine was converted to its difumarate, mp 164.5-167°C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.70 (1H, d), 8.52 (1H, d), 7.94 (1H, d), 7.45 (1H, dd), 6.65 (4H, s), 6.63 (1H, d), 6.49 (1H, dt), 2.96 (2H, t), 2.52 (2H, m).

^{13}C NMR (DMSO-d_6, 75 MHz): δ 167.2, 148.3, 147.7, 134.7, 132.6, 132.5, 128.7, 128.4, 123.7, 38.2, 30.5.

EXAMPLE 7

Sample No. 7 is (E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine Sesquifumarate, which is prepared according to the following procedure.

(E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine is prepared in accordance with the techniques set forth in U.S. Patent Application Serial No. 08/631,762, already incorporated herein by reference in its entirety.

Under a nitrogen atmosphere, fumaric acid (165 mg, 1.18 mmol) was added to a solution of (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine (244 mg, 1.18 mmol) in 2-propanol (15 mL). After stirring 30 min at ambient temperature, the solution was concentrated by rotary evaporation to a light-brown solid. The solid was dissolved in a mixture of 2-propanol (6 mL) and ethanol (1 mL), assisted by warming. The resulting solution was treated with decolorizing carbon, filtered, and cooled at -20°C for 5 days. The crystalline solids were filtered, collected, and dissolved in a mixture of ethanol (3 mL) and methanol (1 mL). This solution was filtered through a sintered glass funnel to remove insoluble matter, and the filtrate was diluted with 2-propanol (4 mL) and cooled at -20°C. The crystalline solids were collected and dried under high vacuum to give 102 mg (26.8%) of (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine sesquifumarate as a light-tan, crystalline powder, mp 126-127°C.

^{1}H NMR (D$_2$O, 300 MHz): δ 8.33 (1H, br s), 8.26 (1H, d, J = 2.4 Hz), 7.97 (1H, t, J = 2.1 Hz), 6.68 (1H, d , J = 16.1 Hz), 6.62 (2H, s), 6.52 (1H, dt, J = 16.1, 7.0 Hz), 4.27 (2H, q, J = 6.9 Hz), 3.24 (2H, t, J = 7.0 Hz), 2.74 (3H, s), 2.70 (2H, m), 1.44 (3H, t, J = 7.0 Hz).

^{13}C NMR (D$_2$O, 75 MHz): δ 175.36, 159.89, 139.88, 137.87, 136.28, 134.56, 132.20, 130.30, 129.07, 68.96, 50.81, 35.73, 32.17, 16.58.

Anal. Calcd for $C_{12}H_{18}N_2O \cdot 1.5\ C_4H_4O_4$: C, 56.83; H, 6.36; N, 7.37. Found: C, 56.88; H, 6.43; N, 7.34.

EXAMPLE 8

Sample No. 8 is (E)-N-Methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine, which is prepared according to the following procedure.

3-Bromo-5-phenylpyridine: A mixture of 3,5-dibromopyridine (15.00 g, 63.3 mmol), phenylboronic acid (8.11 g, 66.5 mmol), sodium carbonate (14.09 g, 133.0 mmol), water (100 mL), toluene (400 mL), absolute ethanol (100 mL), and tetrakis(triphenylphosphine)palladium(0) (3.66 g, 3.17 mmol) was stirred and heated under reflux at 92°C (oil bath temperature) for 19 h. The mixture was cooled to ambient temperature and extracted with dichloromethane (400 mL). The dichloromethane layer was washed with saturated, aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and concentrated to a residue. Vacuum distillation using a short-path apparatus produced 10.58 g of a white solid, bp 70-110°C at 0.05 mm Hg (lit. bp 100-101°C at ~0.1 mm Hg, see Guthikonda, R. N.; DiNinno, F. P. 2-(3-Pyridyl)-carbapenam Antibacterial Agents. U.S. Patent 5,409,920 (Merck and Co., Inc.), 950425). Further purification by column chromatography on silica gel, eluting with hexane-ethyl acetate (5:1, v/v) afforded 8.23 g (55.5%) of 3-bromo-5-phenylpyridine as a white solid, mp 45-46°C, R_f 0.50 (hexane-ethyl acetate (5:1, v/v)).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.74 (1H, d, J = 1.7 Hz), 8.64 (1H, d, J = 1.9 Hz), 8.01 (1H, t, J = 2.0 Hz), 7.56-7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.35, 146.38, 138.27, 136.86, 136.31, 129.20, 128.69, 127.18, 120.91. HRMS: Calcd. for $C_{11}H_8BrN$ (M^+): m/z 232.984010. Found: 232.984177.

(E)-4-[3-(5-Phenylpyridin)yl]-3-buten-1-ol: Under a nitrogen atmosphere, a mixture of 3-buten-1-ol (476 mg, 6.6 mmol), 3-bromo-5-phenylpyridine (1.50 g, 6.4 mmol), palladium(II) acetate (14.4 mg, 0.064 mmol), tri-o-tolylphosphine (78.0 mg, 0.256 mmol), triethylamine (2.5 mL), and acetonitrile (5.0 mL) was stirred and heated under reflux at 90°C (oil bath temperature) for 18 h. Upon cooling to ambient temperature, the mixture was diluted with water (25 mL) and extracted with dichloromethane (4 x 25 mL).

The combined dichloromethane extracts were washed with water (25 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give a dark-green oil (1.69 g). Vacuum distillation using a test-tube apparatus gave 873 mg of a yellow oil, bp 60-80°C at 0.05 mm Hg. Further purification by column chromatography on silica gel (60 g), eluting in succession with hexane-ethyl acetate (5:1, v/v), hexane-ethyl acetate (1:1, v/v), and ethyl acetate afforded 604 mg (41.8%) of (E)-4-[3-(5-phenylpyridin)yl]-3-buten-1-ol as a yellow oil, R_f 0.27 (ethyl acetate).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (1H, d, J = 2.0 Hz), 8.54 (1H, d, J = 1.9 Hz), 7.83 (1H, t, J = 2.1 Hz), 7.58-7.54 (2H, m), 7.49-7.36 (3H, m), 6.54 (1H, d, J = 15.9 Hz), 6.38 (1H, dt, J = 15.9, 6.9 Hz), 3.80 (2H, t, J = 6.3 Hz), 2.53 (2H, dq, J = 6.3, 1.2 Hz), 1.78 (1H, br s).

<u>(E)-N-Methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine:</u> Under a nitrogen atmosphere, a cold (0°C), stirring solution of (E)-4-[3-(5-phenylpyridin)yl]-3-buten-1-ol (577 mg, 2.56 mmol), anhydrous dichloromethane (4 mL), and pyridine (1 drop) was treated with p-toluenesulfonyl chloride (537 mg, 2.82 mmol). The mixture was allowed to warm to ambient temperature. After stirring 17 h, the solution was concentrated by rotary evaporation, and the residue was further dried under high vacuum. The resulting brown gum was dissolved in tetrahydrofuran (5 mL) and 40% aqueous methylamine (5 mL) was added. The solution was stirred 6 h at ambient temperature and was then concentrated by rotary evaporation to a brown gum. The residue was partitioned between 1 M NaOH solution (10 mL) and chloroform (10 mL). The aqueous phase was separated and extracted with chloroform (2 x 10 mL). The combined chloroform extracts were washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give a dark-brown residue. To purify the product, water (25 mL) was added to the residue, and the pH was adjusted to 8.2 with 30% HCl solution. The resulting solution was extracted with dichloromethane (2 x 10 mL); the dichloromethane extracts were subsequently discarded following thin layer chromatography analysis on silica gel. The pH of the

aqueous phase was raised to 12.5 using 30% NaOH solution; the product was extracted with tert-butyl methyl ether (3 x 10 mL). The combined tert-butyl methyl ether extracts were washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give 589 mg of a dark-brown oil. Purification by column chromatography on silica gel, eluting with ethyl acetate produced 95.1 mg of (E)-4-[3-(5-phenylpyridin)yl]-3-buten-1-ol. Subsequent elution with methanol-ammonium hydroxide (9:1, v/v) afforded 82.3 mg (13.5%) of (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine as a dark-brown oil.

^{1}H NMR (CD_3OD, 300 MHz): δ 8.63 (1H, br s), 8.52 (1H, br s), 8.11 (1H, t, J = 1.9 Hz), 7.69-7.65 (2H, m), 7.53-7.40 (3H, m), 6.65 (1H, d, J = 16.0 Hz), 6.52 (1H, dt, J = 15.9, 6.7 Hz), 2.89 (2H, t, J = 6.7 Hz), 2.59-2.49 (2H, m), 2.52 (3H, s). MS (ESI): m/z 239 $(M + H)^+$. HRMS: Calcd. for $C_{16}H_{18}N_2$ (M^+): m/z 238.146999. Found: 238.146600.

EXAMPLE 9

Sample No. 9 is (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-buten-1-amine, which was prepared according to the techniques described in U.S. Patent No. 5,597,919 to Dull et al., the subject matter of which is incorporated herein by reference in its entirety.

COMPARISON EXAMPLE

For comparison purposes, Sample No. C-1 is provided. This sample is (S)-(-)-nicotine, which has been reported to have demonstrated a positive effect towards the treatment of various CNS disorders.

EXAMPLE 10

Determination of Log P Values

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., *J. Med. Chem.* ii:1 (1968)), were calculated

according to methods described in Hopfinger, Conformational Properties of Macromolecules, Academic Press (1973) using Cerius^2 software package by Molecular Simulations, Inc.

EXAMPLE 11

Determination of Binding to Relevant Receptor Sites

Binding of the compounds to relevant receptor sites was determined in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al., the subject matter of which is already incorporated herein by reference in its entirety. Inhibition constants (Ki values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., *Biochem, Pharmacol.* 22:3099 (1973). Data are presented in **Table I**.

EXAMPLE 12

Determination of Dopamine Release

Dopamine release was measured using the techniques described in U.S. Patent No. 5,597,919 to Dull et al., the subject matter of which is already incorporated herein by reference in its entirety. Release is expressed as a percentage of release obtained with a concentration of (S)-(-)-nicotine resulting in maximal effects. Reported EC_{50} is expressed in nM and E_{max} represent the amount released relative to nicotine. Data are presented in **Table I**.

EXAMPLE 13

Determination of Interaction with Muscle

The determination of the interaction of the compounds with muscle receptors was carried out in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al., the subject matter of which is already incorporated herein by reference in its entirety. The muscle tissues employed are representative of cells which do not contain β2 receptors. The maximal activation for individual compounds (E_{max}) was determined as a

percentage of the maximal activation induced by (S)-(-)-nicotine. Data are presented in **Table I.**

EXAMPLE 14

Determination of Interaction with Ganglia

The determination of the interaction of the compounds with ganglionic receptors was carried out in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al., the subject matter of which is already incorporated herein by reference in its entirety. The ganglionic tissues employed are representative of cells which do not contain β2 receptors. The maximal activation for individual compounds (E_{max}) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine. Data are presented in **Table I.**

Table I

Sample No.	Log P	Ki (nM)	Dopamine Release		Muscle Effect (% nicotine)	Ganglion Effect (% nicotine)
			E_{max}	EC_{50} (nM)		
C-1*	0.71	2	100	115	100	100
1	3.22	5	33	4000	12	0
2	1.14	79	107	2400	8	11
3	2.89	21	14	114	5	<15
4	2.43	6	57	61	8	≤15
5	1.22	130	48	16,000	13	0
6	1.38	119	81	5020	15	23
7	2.37	5	70	276	3	≤15
8	3.10	184	≥160	≥100,000	8	0
9	0.32	658	85	2000	4	4

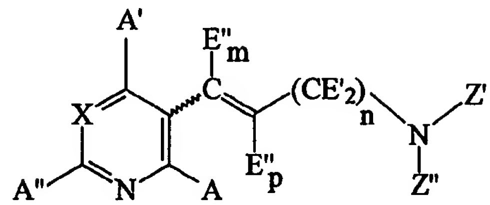
*Sample C-1 is a control and is not an example of the invention.

The data in **Table I** indicate that the compounds have the capability of passing the blood-brain barrier by virtue of their favorable log P values, binding to high affinity CNS nicotinic receptors as indicated by their low binding constants, and activating CNS nicotinic receptors of a subject and causing neurotransmitter release, thereby demonstrating known nicotinic pharmacology. Thus, the data indicate that such compounds have the capability of being useful in treating CNS disorders involving nicotinic cholinergic systems. Furthermore, the data indicate that the compounds do not cause any appreciable effects at muscle sites and ganglionic sites, thus indicating a lack of undesirable side effects in subjects receiving administration of those compounds.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That Which Is Claimed Is:

1. A compound of Formula I:



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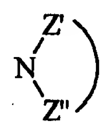
wherein X is C-R′, C-OR′, C-CH_2-OR′ wherein R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; E′ is hydrogen or C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; E″ is C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; Z′ and Z″ are each individually selected from the group consisting of hydrogen, C_1-C_5 alkyl, aryl rings, and can form a ring structure,



A, A′ and A″ are each individually selected from the group consisting of hydrogen, C_1-C_7 alkyl, and halo; m is 0 or 1; p is 0 or 1 with the proviso that when m or p is 0 then that E″ is hydrogen; and the wavy line in the structure represents a cis (Z) or trans (E) form of the compound.

2. The compound according to Claim 1, wherein the compound is (E)-N-methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine;

3. The compound according to Claim 1, wherein the compound is (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine;

4. The compound according to Claim 1 wherein the compound is (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine;

5. The compound according to Claim 1, wherein the compound is (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine.

6. The compound according to Claim 1, wherein the compound is (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine.

7. The compound according to Claim 1, wherein X is C-R′; R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; n is an integer which ranges from 1 to 3; Z′ and Z″ individually represent hydrogen, methyl or isopropyl; A and A′ represent hydrogen; A″ represents hydrogen, methyl or ethyl; m is 0 and p is 0.

8. The compound according to Claim 1, wherein X is C-OR′; R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; n is an integer which ranges from 1 to 3; Z′ and Z″ individually represent hydrogen, methyl or isopropyl; A and A′ represent hydrogen; A″ represents hydrogen, methyl or ethyl, m is 0 and p is 0.

9. The compound according to Claim 1, wherein X is C-CH_2-OR′, R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; n is an integer which ranges from 1 to 3; Z′ and Z″ individually represent hydrogen, methyl or isopropyl; A and A′ represent hydrogen; A″ represents hydrogen, methyl or ethyl, m is 0 and p is 0.

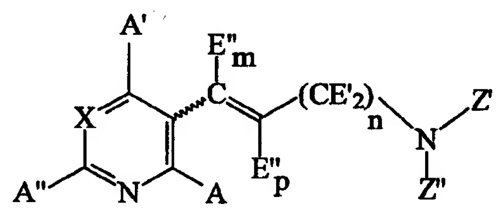
10. A pharmaceutical composition comprising a compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10, comprising said compound in an amount effective to treat a central nervous system disorder characterized by a decrease in nicotinic receptor activity.

12. A pharmaceutical composition according to claim 10, comprising said compound in an amount effective to treat a neurodegenerative central nervous system disorder.

13. A pharmaceutical composition according to claim 10, comprising said compound in an amount effective to treat a central nervous disorder selected from the group consisting of Parkinsonism, Parkinson's Disease, Tourette's Syndrome, attention deficit disorder, schizophrenia, and senile dementia of the Alzheimer's type.

14. The use of a compound having the formula:



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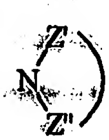
for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein X is C-R′, C-OR′, C-CH_2-OR′ wherein R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; E′ is hydrogen or C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; E″ is C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; Z′ and Z″ are each individually selected from the group consisting of hydrogen, C_1-C_5 alkyl, aryl rings, and can form a ring structure,

[illegible]



A, A′ and A″ are each individually selected from the group consisting of hydrogen, C_1-C_7 alkyl, and halo; m is 0 or 1; p is 0 or 1 with the proviso that when m or p is 0 then that E″ is hydrogen; and the wavy line in the structure represents a cis (Z) or trans (E) form of the compound.

15. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein said central nervous system disorder is a neurodegenerative disease.

16. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the central nervous system disorder is selected from the group consisting of Parkinsonism, Parkinson's Disease, Tourette's Syndrome, attention deficit disorder, schizophrenia, and senile dementia of the Alzheimers type.

17. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the compound is (E)-N-methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine.

18. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the compound is (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine.

19. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the compound is (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine.

20. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the compound is (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine.

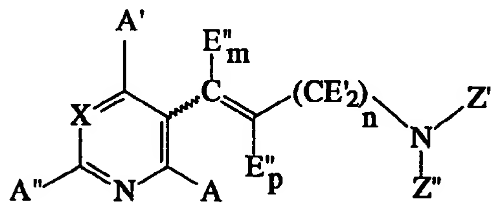
21. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the compound is (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine.

22. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the amount effective to prevent or treat said central nervous disorder is at least about 25 mg / patient / 24 hours and does not exceed about 500 mg / patient / 24 hours.

23. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the amount effective to prevent or treat said central nervous system disorder is at least about 10 mg / patient / 24 hours and does not exceed about 400 mg / patient / 24 hours.

24. The use of a compound of Claim 14 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the amount of the compound of formula I administered is such that the subject does not experience a concentration of compound in plasma which exceeds 500 ng/ml.

25. A method for providing prevention or treatment of a central nervous system disorder comprising administering to a subject in need thereof, an effective amount of a compound of the formula:



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wherein X is C-R′, C-OR′, C-CH_2-OR′ wherein R′ is selected from the group consisting of H, C_1-C_5 alkyl, an aromatic group containing species and alkyl-, halo-, or amino- substituted aromatic group containing species; E′ is hydrogen or C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; E″ is C_1-C_5 alkyl or halo substituted C_1-C_5 alkyl; Z′ and Z″ are each individually selected from the group consisting of hydrogen, C_1-C_5 alkyl, aryl rings, and can form a ring structure,

A, A′ and A″ are each individually selected from the group consisting of hydrogen, C_1-C_7 alkyl, and halo; m is 0 or 1; p is 0 or 1 with the proviso that when m or p is 0 then that E″ is hydrogen; and the wavy line in the structure represents a cis (Z) or trans (E) form of the compound; wherein said compound is administered in an amount effective to prevent or treat said central nervous system disorder.

26. The method according to Claim 25, wherein said CNS disorder is a neurodegenerative disease.

27. The method according to Claim 25, wherein the central nervous system disorder is selected from the group consisting of Parkinsonism, Parkinson's Disease, Tourette's Syndrome, attention deficit dis rder, schizophrenia, and senile dementia of the Alzheimers type.

28. The method according to Claim 25, wherein the compound is (E)-N-methyl-4-[3-(5-benzyloxypyridin)yl]-3-buten-1-amine.

29. The method according to Claim 25, wherein the compound is (E)-N-methyl-4-[3-(5-phenoxypyridin)yl]-3-buten-1-amine.

30. The method according to Claim 25, wherein the compound is (E)-N-methyl-4-[3-(5-isopropoxypyridin)yl]-3-buten-1-amine.

31. The method according to Claim 25, wherein the compound is (E)-N-methyl-4-[3-(5-methoxymethylpyridin)yl]-3-buten-1-amine.

32. The method according to Claim 25, wherein the compound is (E)-N-methyl-4-[3-(5-phenylpyridin)yl]-3-buten-1-amine.

33. The method according to Claim 25, wherein the amount effective to prevent or treat said central nervous system disorder is at least about 25 mg / patient / 24 hours and does not exceed about 500 mg / patient / 24 hours.

34. The method according to Claim 25, wherein the amount effective to prevent or treat said central nervous system disorder is at least about 10 mg / patient / 24 hours and does not exceed about 400 mg / patient / 24 hours.

35. The method according to Claim 25, wherein the amount of the compound of formula I administered is such that the subject does not experience a concentration of compound in plasma which exceeds 500 ng/ml.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/03091

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/64 C07D213/61 C07D213/38 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 20929 A (REYNOLDS TOBACCO CO R ;UNIV KENTUCKY RES FOUND (US); CROOKS PETER) 11 July 1996 see compound IX	1-35
X	WO 96 20600 A (REYNOLDS TOBACCO CO R ;BENCHERIF MEROUANE (US); LIPPIELLO PATRICK) 11 July 1996 see the whole document	1-35
X,P	US 5 616 716 A (DULL GARY M ET AL) 1 April 1997 see the whole document	1-35
X	WO 95 28400 A (GLAXO GROUP LTD ;NORTH PETER CHARLES (GB); WADMAN SJOERD NICOLAAS) 26 October 1995 see the whole document	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 May 1998	04.06.98

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte ional application No.

PCT/US 98/03091

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25-35
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 25-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

. .ormation on patent family members

Interr   ıal Application No
PCT/US 98/03091

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			US	5731314 A	24-03-1998
			AU	4610896 A	24-07-1996
			EP	0801527 A	22-10-1997
US 5616716	A	01-04-1997	NONE		
WO 9528400	A	26-10-1995	AU	2343995 A	10-11-1995

Form PCT/ISA/210 (patent family annex) (July 1992)

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(74) Agents: BODENHEIMER, Stephen, M., Jr. et al.; Bell, Seltzer, Park & Gibson, P.O. Drawer 34009, Charlotte, NC 28234 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract

Patients susceptible to or suffering from central nervous system disorders are treated by administering an effective amount of an aryl substituted olefinic amine compound or an aryl substituted acetylenic compound. Exemplary compounds are (E)-N-methyl-4-[3-(6-methylpyrindin)yl]-3-butene-1-amine and N-methyl-4-(3-pyridinyl)-3-butyne-1-amine.

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CF	Central African Republic		of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
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GA	Gabon	MR	Mauritania	VN	Viet Nam

PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

Background of the Invention

The present invention relates to compounds having pharmaceutical properties, and in particular, to compounds useful for preventing and treating central nervous system (CNS) disorders. The present invention relates to a method for treating patients suffering from or susceptible to such disorders, and in particular, to a method for treating patients suffering from those disorders which are associated with neurotransmitter system dysfunction. The present invention also relates to compositions of matter useful as pharmaceutical compositions in the prevention and treatment of CNS disorders which have been attributed to neurotransmitter system dysfunction.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia (early onset Alzheimer's disease), senile dementia

(dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning, orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a neurotransmitter involved in learning and memory mechanisms). See, Jones, et al., Intern. J. Neurosci., Vol. 50, p. 147 (1990); Perry, Br. Med. Bull., Vol. 42, p. 63 (1986) and Sitaram, et al., Science, Vol. 201, p. 274 (1978). It has been observed that nicotinic acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. See, Giacobini, J. Neurosci. Res., Vol. 27, p. 548 (1990); and Baron, Neurology, Vol. 36, p. 1490 (1986). As such, it would seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Certain attempts have been made to treat SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such rec ptors upon chronic administration to animals. Se , Rowell, Adv. Behav. Biol., Vol. 31, p. 191 (1987); and Marks, J. Pharmacol. Exp. Ther., Vol. 226, p. 817 (1983). It also has been

propos d that nicotine can act directly to elicit the release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. See, Rowell, et al., J. Neurochem., Vol. 43, p. 1593 (1984); Sherwood, Human Psychopharm., Vol. 8, pp. 155-184 (1993); Hodges, et al., Bio. of Nic., Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., Br. J. Psych., Vol. 154, p. 797 (1989); and U.S. Patent Nos. 4,965,074 to Leeson and 5,242,935 to Lippiello et al. Other methods for treating SDAT have been proposed, including U.S. Patent Nos. 5,212,188 to Caldwell et al. and 5,227,391 to Caldwell et al. and European Patent Application No. 588,917. Another proposed treatment for SDAT is Cognex, which is a capsule containing tacrine hydrochloride, available from Parke-Davis Division of Warner-Lambert Company, which reportedly preserves existing acetylchloine levels in patients treated therewith.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. See, Rinne, et al., Brain Res., Vol. 54, pp. 167-170 (1991) and Clark, et al., Br. J. Pharm., Vol. 85, pp. 827-835 (1985). It also has been proposed that nicotine can ameliorate the symptoms of PD. See, Smith et al., Rev. Neurosci., Vol. 3(1), pp. 25-43 (1982).

Certain ttempts have be n made to treat PD. One proposed tr atment for PD is Sinemet CR, which is a sustained-releas tablet containing a mixture of carbidopa and levodopa, available from The DuPont Merck

Pharmaceutical Co. Another proposed treatment for PD is Eldepryl, which is a tablet containing selefiline hydrochloride, available from Somerset Pharmaceuticals, Inc. Another proposed treatment for PD is Parlodel, which is a tablet containing bromocriptine mesylate, available from Sandoz Pharmaceuticals Corporation. Another method for treating PD and a variety of other neurodegenerative diseases has been proposed in U.S. Patent No. 5,210,076 to Berliner et al.

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of neurological and behavioral symptoms. Typical symptoms include (i) the onset of the disorder before the age of 21 years, (ii) multiple motor and phonic tics although not necessarily concurrently, (iii) variance in the clinical phenomenology of the tics, and (iv) occurrence of quasi daily tics throughout a period of time exceeding a year. Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing; while phonic or vocal tics include throat clearing, sniffling, yelping, tongue clicking and uttering words out of context. The pathophysiology of TS presently is unknown, however it is believed that neurotransmission dysfunction is implicated with the disorder. See, Calderon-Gonzalez et al., Intern. Pediat., Vol. 8(2), pp. 176-188 (1993) and Oxford Textbook of Medicine, Eds. Weatherall et al., Chapter 21.218 (1987).

It has been proposed that nicotine pharmacology is beneficial in suppressing the symptoms associated with TS. See, Devor et al., The Lancet, Vol. 8670, p. 1046 (1989); Jarvik, British J. of Addiction, Vol. 86, pp. 571-575 (1991); McConville et al., Am. J. Psychiatry, Vol. 146 (6), pp. 793-794 (1991); Newhous et al., Brit. J. Addic., Vol. 86, pp. 521-526 (1991); McConville et al., Biol. Psychiatry, Vol. 31, pp. 832-840 (1992); and Sanberg et al.,

Proceedings from Intl. Symp. Nic., S39 (1994). It also has been proposed to treat TS using Haldol, which is haloperidol available from McNeil Pharmaceutical; Catapres, which is clonidine available from Boehringer Ingelheim Pharmaceuticals, Inc., Orap, which is pimozide available from Gate Pharmaceuticals; Prolixin, which is fluphenazine available from Apothecon Division of Bristol-Myers Squibb Co.; and Klonopin, which is clonazepam available from Hoffmann-LaRoche Inc.

Attention deficit disorder (ADD) is a disorder which affects mainly children, although ADD can affect adolescents and adults. See, Vinson, Arch. Fam. Med., Vol. 3(5), pp. 445-451 (1994); Hechtman, J. Psychiatry Neurosci., Vol. 19 (3), pp. 193-201 (1994); Faraone et al., Biol. Psychiatry, Vol. 35(6), pp. 398-402 (1994) and Malone et al., J. Child Neurol., Vol. 9(2), pp. 181-189 (1994). Subjects suffering from the disorder typically have difficulty concentrating, listening, learning and completing tasks; and are restless, fidgety, impulsive and easily distracted. Attention deficit disorder with hyperactivity (ADHD) includes the symptoms of ADD as well as a high level of activity (e.g., restlessness and movement). Attempts to treat ADD have involved administration of Dexedrine, which is a sustained release capsule containing detroamphetamine sulfate, available from SmithKline Beecham Pharmaceuticals; Ritalin, which is a tablet containing methylphenidate hydrochloride, available from Ciba Pharmaceutical Company; and Cylert, which is a tablet containing pemoline, available from Abbott Laboratories. In addition, it has been reported that administration of nicotine to an individual improves that individual's selective and sustained attention. See, Warburton et al., Cholinergic control of cognitive resources, Neuropsychobiology, Eds. M ndl wicz, et al., pp 43-46 (1993).

Schizophrenia is characterized by psychotic symptoms including delusions, catatonic behavior and prominent hallucinations, and ultimately results in a profound decline in the psychosocial affect of the subject suffering therefrom. Traditionally, schizophrenia has been treated with Klonopin, which is available as a tablet containing clonezepam, available from Hoffmann-LaRoche Inc.; Thorazine, which is available as a tablet containing chlorpromazine, available from SmithKline Beecham Pharmaceuticals; and Clozaril, which is a tablet containing clozapine, available from Sandoz Pharmaceuticals. Such neuroleptics are believed to be effective as a result of interaction thereof with the dopaminergic pathways of the CNS. In addition, a dopaminergic disfunction possessed by individuals suffering from schizophrenia has been proposed. See, Lieberman et al., Schizophr. Bull., Vol. 19, pp. 371-429 (1993) and Glassman, Amer. J. Psychiatry, Vol. 150, pp. 546-553 (1993). Nicotine has been proposed as being effective in effecting neurotransmitter dysfunction associated with schizophremia. See, Merriam et al., Psychiatr. Annals, Vol. 23, pp. 171-178 (1993) and Adler et al., Biol. Psychiatry, Vol. 32, pp. 607-616 (1992).

Nicotine has been proposed to have a number of pharmacological effects. Certain of those effects may be related to effects upon neurotransmitter release. See, for example, Sjak-shie et al., Brain Res., Vol. 624, pp. 295-298 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported by Rowell et al., J. Neurochem., Vol. 43, pp. 1593-1598 (1984); Rapier et al., J. Neurochem., Vol. 50, pp. 1123-1130 (1988); Sandor et al., Brain Res., Vol. 567, pp. 313-316 (1991) and Vizi, Br. J. Pharmacol., Vol. 47, pp. 765-777 (1973). Release of norepinephrine by neurons

upon administration of nicotine has been reported by Hall et al., Biochem. Pharmacol., Vol. 21, pp. 1829-1838 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., Arch. Int. Pharmacodyn. Ther., Vol. 296, pp. 91-97 (1977). Release of glutamate by neurons upon administration of nicotine has been reported by Toth et al., Neurochem Res., Vol. 17, pp. 265-271 (1992). Therefore, it would be desirable to provide a pharmaceutical composition containing an active ingredient having nicotinic pharmacology, which pharmaceutical composition is capable of illicting neurotransmitter release within a subject in order to prevent or treat a neurological disorder. In addition, nicotine reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used for the treatment of certain CNS disorders. See, Sanberg et al., Pharmacol. Biochem. & Behavior, Vol. 46, pp. 303-307 (1993); Harsing et al., J. Neurochem., Vol. 59, pp. 48-54 (1993) and Hughes, Proceedings from Intl. Symp. Nic., S40 (1994). Furthermore, various other beneficial pharmacological effects of nicotine have been proposed. See, Decina et al., Biol. Psychiatry, Vol. 28, pp. 502-508 (1990); Wagner et al., Pharmacopsychiatry, Vol. 21, pp. 301-303 (1988); Pomerleau et al., Addictive Behaviors, Vol. 9, p. 265 (1984); Onaivi et al., Life Sci., Vol. 54(3), pp. 193-202 (1994) and Hamon, Trends in Pharmacol. Res., Vol. 15, pp. 36-39.

It would be desirable to provide a useful method for the prevention and treatment of a CNS disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a disorder. It would be highly beneficial to provide individuals suffering from certain CNS disorders with interruption of the symptoms of those diseases by the administration of a pharmaceutical composition which

has nicotinic pharmacology and which has a ben ficial effect upon the functioning of the CNS, but which does not provide any significant associated side effects (e.g., increased heart rate and blood pressure) attendant with interaction of that compound with cardiovascular sites. It would be highly desirable to provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors which have the potential to affect the functioning of the CNS, but which does not significantly affect those receptors which have the potential to induce undesirable side effects (e.g., appreciable pressor cardiovascular effects and appreciable activity at skeletal muscle sites).

Summary of the Invention

The present invention relates to aryl substituted aliphatic amine compounds, aryl substituted olefinic amine compounds and aryl substituted acetylenic amine compounds.

The present invention relates to a method for providing prevention or treatment of a central nervous system (CNS) disorder. The method involves administering to a subject an effective amount of a compound of the present invention.

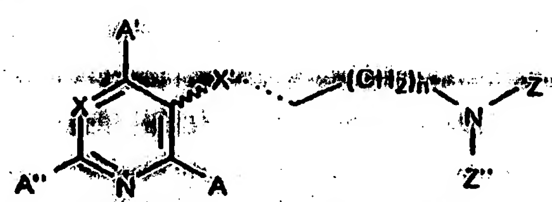
The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a compound of the present invention. Such a pharmaceutical composition incorporates a compound which has the capability of interacting with relevant nicotinic receptor sites of a subject, and hence has the capability of acting as a therapeutic in the prevention or treatment of a CNS disorder.

Th pharmaceutical compositions of the present invention are useful for the prevention and treatment of CNS disorders. The pharmaceutical

compositions provide therapeutic benefit to individuals suffering from certain CNS disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions have the potential to (i) exhibit nicotinic pharmacology and affect nicotinic receptors sites in the CNS (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) not provide appreciable adverse side effects (e.g., significant increases in blood pressure and heart rate, and significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of CNS disorders.

<u>Detailed Description of the Preferred Embodiments</u>

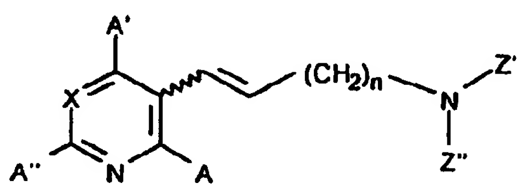
The present invention, in one aspect, relates to certain compounds having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and ven greater than 0.3; less than 0 and generally less than -0.1; or 0; as determined in accordance with Hansch et al., <u>Chem. Rev.</u>, Vol. 91, pp.

165-195 (1991); n is an integer which can range from 1 to 5, preferably from 1 to 3, and most preferably is 2 or 3; Z′ and Z′′ individually represent hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, such as methyl, ethyl or isopropyl), and preferably at least one of Z′ and Z′′ is hydrogen; A, A′ and A′′ individually represent hydrogen, alkyl (e.g., lower straight chain or branched alkyl, including C_1 - C_7, but preferably methyl or ethyl) or halo (e.g., F, Cl, Br or I); the dashed line in the structure represents a C-C single bond, a C-C double bond or a C-C triple bond; the wavy line in the structure represents a cis (Z) or trans (E) form of the compound when the dashed line is a C-C double bond; and X′ represents CH_2 when the dashed line is a C-C single bond, CH when the dashed line is a C-C double bond, and C when the dashed line is a C-C triple bond. X includes N, C-H, C-F, C-Cl, C-Br, C-I, C-NR′R′′, C-CF_3, C-OH, C-CN, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR′, C-C(=O)NR′R′′, C-NR′C(=O)R′, C-C(=O)OR′, C-OC(=O)R′, C-OC(=O)NR′R′′ and C-NR′C(=O)OR′ where R′ and R′′ are individually hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, preferably methyl or ethyl). When X represents a carbon atom bonded to a substituent species, that substituent species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In certain circumstances when X represents a carbon atom bonded to a substituent species, the dashed line is a C-C double bond and the compound has the trans (E) form, the substituent species is characterized as having a sigma m value not equal to 0. Particularly when the dashed line is a C-C double bond, th compound has the trans (E) form, A, A′, A′′ and Z′ all are hydrogen, n is 2, and Z′′ is methyl, the substituent species is characterized as having a sigma m value not equal to 0. In addition, it is highly

pref rred that A is hydrogen, it is preferred that A′ is hydrogen, and normally A′′ is hydrogen. Generally, both A and A′ are hydrogen; sometimes A and A′ are hydrogen, and A′′ is methyl or ethyl; and often A, A′ and A′′ are all hydrogen. One representative compound is N-methyl-4-(3-pyridinyl)-butane-1-amine for which for which the dashed line is a C-C single bond, X′ is CH_2, X is C-H, n is 2, and A, A′, A′′ and Z′ each are hydrogen, and Z′′ is methyl. Another representative compound is N-methyl-4-(3-pyridinyl)-3-butyne-1-amine for which for which the dashed line is a C-C triple bond, X′ is C, X is C-H, n is 2, and A, A′, A′′ and Z′ each are hydrogen, and Z′′ is methyl. Other representative compounds are (Z)-metanicotine and (E)-metanicotine, for which the dashed line is a C-C double bond, X′ is CH, n is 2, and A, A′, A′′ and Z′ each are hydrogen, and Z′′ is methyl. Of particular interest are compounds having the formula:



where n, X, A, A′, A′′, Z′ and Z′′ are as defined hereinbefore, and those compounds can have the cis (Z) or trans (E) form. For such compounds of particular interest, X most preferably is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0. One representative compound is (E)-4-(5-pyrimidinyl)-3-but ne-1-amine for which X is N, n is 2, and A, A′, A′′, Z′ and Z′′ each are hydrogen. Another r pr sentative compound is (E)-4-[3-(5-methoxypyridin)yl]-3-but ne-1-amin for which X is C-

OCH_3, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine for which X is N, n is 2, A, A', A'', and Z' are each hydrogen, and Z'' is methyl. Another representative compound is (E)-N-methyl-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, and A, A', A'', and Z' are each hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-ethoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_2CH_3, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_2CH_3, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-aminopyridin)yl]-3-butene-1-amine for which X is C-NH_2, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine for which X is C-NH_2, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-bromopyridin)yl]-3-butene-1-amine for which X is C-Br, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine for which X is C-Br, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-methoxy-6-methylpyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, A'' is methyl, and A, A', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-methoxy-6-methylpyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, A'' and Z'' each are methyl, and A, A' and Z' each ar hydrogen. Another representative compound is (E)-N-methyl-4-[3-(6-methylpyridin)yl]-3-butene-1-amin for which X is C-H, n is 2, A'' and Z''

each are m thyl, and A, A′ and Z′ each are hydrogen. Another representative compound is (E)-4-[3-(6-methylpyridin)yl]-3-butene-1-amine for which X is C-H, n is 2, A′′ is methyl, and A, A′, Z′ and Z′′ each are hydrogen. Another representative compound is (E)-N-methyl-5-[3-pyridinyl]-4-pentene-1-amine for which X is C-H, n is 3, Z′′ is methyl, and A, A′, A′′ and Z′ are each hydrogen. Another representative compound is (E)-N-(2-propyl)-4-[3-pyridynyl]-3-butene-1-amine for which X is C-H, n is 2, Z′′ is isopropyl, and A, A′, A′′ and Z′ are each hydrogen.

The manner in which aryl substituted aliphatic amine compounds of the present invention are synthetically produced can vary. Preparation of various aryl substituted aliphatic amine compounds can be carried out using the types of techniques disclosed by Rondahl, <u>Acta Pharm. Suec.</u>, Vol. 13, pp. 229-234 (1976). Certain metanicotine-type compounds that possess a saturated side chain rather than an olefinic side chain can be prepared by hydrogenation of the corresponding metanicotine-type compounds or the corresponding acetylenic precursors. For example, dihydrometanicotine can be prepared by hydrogenation of (E)-metanicotine as described by Kamimura et al., <u>Agr. Biol. Chem.</u>, Vol. 27, No. 10, pp. 684-688 (1963).

The manner in which aryl substituted acetylenic amine compounds of the present invention are synthetically produced can vary. For example, an aryl substituted acetylenic amine compound, such N-methyl-4-(3-pyridinyl)-3-butyne-1-amine, can be prepared using a number of synthetic steps: (i) conversion of 3-pyridinecarboxaldehyde to a 1,1-dihalo-2-(3-pyridinyl)-ethylene using a carbon tetrahalide and triphenylphosphine, (ii) side chain elaboration of this intermediate by reaction with butyl lithium and thylen oxid , affording 4-(3-pyridinyl)-3-butyn-1-ol, (iii) conversion of this intermediat to its

methanesulfonate ester, and (iv) mesylate displacement with methyl amine, affording N-methyl-4-(3-pyridinyl)-3-butyne-1-amine.

The manner in which aryl substituted olefinic amine compounds of the present invention are synthetically produced can vary. (E)-metanicotine can be prepared using the techniques set forth by Löffler et al., Chem. Ber., Vol. 42, pp. 3431-3438 (1909) and Laforge, J.A.C.S., Vol. 50, p. 2477 (1928). Certain novel 6-substituted metanicotine-type compounds can be prepared from the corresponding 6-substituted nicotine-type compounds using the general methods of Acheson et al., J. Chem. Soc., Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The requisite precursors for such compounds, 6-substituted nicotine-type compounds, can be synthesized from 6-substituted nicotinic acid esters using the general methods disclosed by Rondahl, Acta Pharm. Suec., Vol. 14, pp 113-118 (1977). Preparation of certain 5-substituted metanicotine-type compounds can be accomplished from the corresponding 5-substituted nicotine-type compounds using the general method taught by Acheson et al., J. Chem. Soc., Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The 5-halo nicotine-type compounds (e.g., fluoro and bromo nicotine-type compounds) and the 5-amino nicotine-type compounds can be prepared using the general procedures disclosed by Rondahl, Act. Pharm. Suec., Vol. 14, pp. 113-118 (1977). The 5-trifluoromethyl nicotine-type compounds can be prepared using the techniques and materials set forth in Ashimori et al., Chem. Pharm. Bull., Vol. 38(9), pp. 2446-2458 (1990) and Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977). Furthermore, preparation of certain metanicotine-type compounds can be accomplished using a palladium catalyzed coupling reaction of an aromatic halide and a terminal ol fin containing a protected amine substituent, removal of the protective group to obtain

a primary amine, and optional alkylation to provide a secondary or tertiary amine. In particular, certain metanicotine-type compounds can be prepared by subjecting a 3-halo substituted, 5-substituted pyridine compound or a 5-halo substituted pyrimidine compound to a palladium catalyzed coupling reaction using an olefin possessing a protected amine functionality (e.g., such an olefin provided by the reaction of a phthalimide salt with 3-halo-1-propene, 4-halo-1-butene, 5-halo-1-pentene or 6-halo-1-hexene). See, Frank et al., J. Org. Chem., Vol. 43(15), pp. 2947-2949 (1978) and Malek et al., J. Org. Chem., Vol. 47, pp. 5395-5397 (1982). Alternatively, certain metanicotine-type compounds can be prepared by coupling an N-protected, modified amino acid residue, such as 4-(N-methyl-N-tert-butyloxycarbonyl)aminobutyric acid methyl ester, with an aryl lithium compound, as can be derived from a suitable aryl halide and butyl lithium. The resulting N-protected aryl ketone is then chemically reduced to the corresponding alcohol, converted to the alkyl halide, and subsequently dehydrohalogenated to introduce the olefin functionality. Removal of the N-protecting group affords the desired metanicotine-type compound. There are a number of different methods for providing (Z)-metanicotine-type compounds. In one method, (Z)-metanicotine-type compounds can be synthesized from nicotine-type compounds as a mixture of E and Z isomers; and the (Z)-metanicotine-type compounds can then be separated by chromatography using the types of techniques disclosed by Sprouse et al., Abstracts of Papers, p. 32, Coresta/TCRC Joint Conference (1972). In another method, (Z)-metanicotine can be prepared by the controlled hydrogenation of the corresponding acetylenic compound (e.g., N-methyl-4-(3-pyridinyl)-3-butyne-1-amine). For example, certain 5-substituted (Z)-metanicotine-type compounds and certain 6-substituted (Z)-metanicotine-type compounds can be

prepared from 5-substituted-3-pyridinecarboxaldehydes and 6-substituted-3-pyridinecarboxaldehydes, respectively.

A representative compound, (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine, can be synthesized using the following representative procedure. 5-Bromonicotine (0.018 mole) in 10 ml of methylene chloride dried over phosphorous pentaoxide has a solution of ethyl chloroformate (0.018 mole) in 10 mL of similarly dried methylene chloride added dropwise over 10 to 15 minutes. The resulting mixture then is refluxed under nitrogen atmosphere for about 3 hours. Then, the methylene chloride is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield a N-ethylcarbamate derivative of 5-bromometanicotine product as a thick liquid which has a boiling point of 182°C at 0.04 mm Hg. This product (0.08 mole) is then refluxed for several hours in 15 ml of concentrated aqueous hydrochloric acid. The resulting reaction mixture was cooled and basified to pH 8-9 using concentrated aqueous sodium hydroxide while the mixture is maintained at a temperature of about 0°C. The resulting product is extracted four times with 20 ml quantities of chloroform, and the combined collected fractions are dried over anhydrous sodium sulfate. Then, the chloroform is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield the (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine product as a colorless liquid which has a boiling point of 115°C at 0.04 mm Hg. That product can be converted to a fumarate salt, which has a melting point of 148-150°C.

A representative compound, (E)-N-methyl-5-[3-pyridinyl]-4-p ntene-1-amine, can be synthesized using the following representative procedure. A solution of N-methyl anabasine (0.011 mole) in 100 mL methylene

chloride is added dropwise into a slight molar xcess of ethyl chloroformate in 100 mL methylene chloride under nitrogen atmosphere in a flask equipped with a condenser. Then, the mixture is refluxed for about 3 hours. Then, the methylene chloride is removed using a rotary evaporator, and the remaining material is distilled using a short-path distillation apparatus to yield N-ethylcarbamate of trans-homometanicotine product as a colorless liquid which has a boiling point of 170-172°C at 1 mm Hg. This product (0.012 mole) is dissolved in 50 mL concentrated aqueous hydrochloric acid, and the resulting mixture is refluxed overnight. The reaction mixture then is cooled. The resulting product is extracted four times with 20 mL quantities of chloroform, and the combined collected fractions are dried over anhydrous sodium sulfate. Then, the chloroform is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield the (E)-N-methyl-5-[3-pyridinyl]-4-pentene-1-amine product as a colorless liquid which has a boiling point of 81-82°C at 4 mm Hg. That product can be converted to a fumarate salt, which has a melting point of 139-140°C.

A representative compound, (E)-N-(2-propyl)-4-[3-pyridynyl]-3-butene-1-amine, can be synthesized using the following representative procedure. (E)-4-[3-pyridynyl]-3-butene-1-amine (0.5 millimole) is prepared according to the procedure of Heck, J. Org. Chem., Vol. 43, pp. 2947 (1978), combined with 2-iodopropane (0.525 millimole) and potassium carbonate (1 millimole), and refluxed in 30 mL tetrahydrofuran for 36 hours. Then, the tetrahydrofuran is removed using a rotary evaporator and 5 mL ethyl ether is added to the remaining residue. Filtration followed by concentration on a rotary evaporator yi lds a brown oil which can be purified by column chromatography followed by distillation under reduced pressure (138-140°C at

0.25 mm Hg) to yield the (E)-N-(2-propyl)-4-[3-pyridynyl]-3-butene-1-amine product.

A representative compound, (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine, can be synthesized using the following representative procedure. 5-Amino nicotine (1 millimole) is prepared according to the procedure of Rondahl, Acta. Pharm. Suec., Vol. 14, pp. 113 (1977), combined with phthalic anhydride (1 millimole), and refluxed in 3 mL toluene for 16 hours using a Dean-Stark trap. The reaction mixture is cooled to ambient temperature and the toluene is removed using a rotary evaporator. To the remaining residue is added 2 mL methylene chloride, followed by dropwise addition of ethyl chloroformate (1.1 millimole) under nitrogen atmosphere. The resulting mixture is refluxed for 8 hours, cooled to ambient temperature, and concentrated on a rotary evaporator. The resulting viscous oil is heated to 160°C under vacuum for one hour, and then cooled to ambient temperature. Then, 10 mL of a 10 percent aqueous solution of sodium bicarbonate is added to the reaction mixture. That mixture then is extracted three times with 15 mL portions of chloroform. The combined portions then are dried over anhydrous potassium carbonate. Filtration followed by evaporation of chloroform yields a pale brown oil. This oil is dissolved in 1 mL tetrahydrofuran followed by 2 mL of a solution 2 parts methyl amine in 3 parts water. This mixture is stirred for 10 hours. Then, tetrahydrofuran and excess methyl amine are removed using a rotary evaporator. Concentrated aqueous hydrochloric acid (5 mL) is added to the reaction mixture followed by reflux for several hours. The acidic solution, after cooling to ambient temperature, is xtracted three times with 10 mL portions of ethyl acetat . Then, the acidic solution is basified using potassium carbonate and then sodium hydroxid . The basic solution th n is

extracted four times with 10 mL portions of n-butyl alcohol. The combined extracts are dried over anhydrous magnesium sulfate. Filtration, followed by concentration on a rotary evaporator yields the (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine product as a dark brown oil. The product can be purified by column chromatography using a chloroform:methanol:triethylamine (60:20:20) solvent system as an eluent.

The present invention relates to a method for providing prevention of a CNS disorder to a subject susceptible to such a disorder, and for providing treatment to a subject suffering from a CNS disorder. In particular, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of the CNS disorder (i.e., provide protective effects), amelioration of the symptoms of the CNS disorder, and amelioration of the reoccurrence of the CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. The compounds normally are not optically active. However, certain compounds can possess substituent groups of a character so that those compounds possess optical activity. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts, such as chloride, perchlorate, ascorbate, sulfate, tartrate, fumarate, citrate, malate, lactate or aspartate salts). CNS disorders which can be treated in accordance with the present invention include presenile d mentia (early ons t Alzheimer's disease), senile dem ntia (dementia of the

Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics, steroids and corticosteroids.

Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular CNS disorder.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al.); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carri r); intravenously (.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmac utically acceptable liquid or mixture of liquids); or

transdermally (e.g., using a transd rmal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Ciba-Geigy Corporation and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, such as a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that effect the functioning of the CNS.

The dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder. Thus, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to licit neuropharmacological effects (e.g., licit neurotransmitter secretion, thus resulting in effectiv prevention or treatment of the

disorder). Prev ntion of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than -0.5, often are greater than about 0, and frequently are greater than about 0.5. The log P values of such typical compounds generally are less than about 3.0, often are less than about 2.5, and frequently are less than about 2.0. Log P values provide a measure of the ability of a compound to pass across a diffusion

barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and in most circumstances, cause activation of, nicotinic cholinergic receptors of the brain of the patient. As such, such compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally exceed about 1 nM, often exceed about 200 nM, and frequently exceed about 500 nM. The receptor binding constants of such typical compounds generally are less than about 10 uM, often are less than about 7 uM, and frequently are less than about 2 uM. Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively eliciting neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, such compounds have the ability to cause relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds useful in carrying out the present invention provide for the secretion of dopamine in amounts of at least about 25 percent, often at least about 50 percent, and frequently at least about 75 percent, of that elicited by an equal molar amount of S(-) nicotine. Certain compounds of the present invention can provide secretion of dopamine in an amount which can exceed that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from muscle preparations. Thus, such compounds exhibit receptor activation constants or EC50 values (i.e., which provide a measure of the concentration of compound needed to activate half of the relevant receptor sites of the skeletal muscle of a patient) which are relatively high. Generally, typical compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue. As such, such compounds have poor ability to caus isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, typical compounds useful

in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the reoccurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as demonstrated by increased effects relating to the cardiovascular system, and effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/5, and often less than 1/10, that amount sufficient to cause any side effects to a significant degree.

The following example is provided in order to further illustrate various embodiments of the invention but should not be construed as limiting the scope thereof. Unless otherwise noted, all parts and percentages are by weight.

EXAMPLE

Sample No. 1 is (E)-4-(5-pyrimidinyl)-3-butene-1-amine monofumarate (compound III monofumarate), which was prepared essentially in accordance with the following techniques.

<u>N-3-Butene-1-phthalimide (I)</u>:

This compound was prepared essentially in accordance with the techniques described in Heck, et al., <u>J. Org. Chem.</u>, Vol. 43, pp. 2947-2949 (1978).

<u>(E)-N-[4-(5-Pyrimidinyl)-3-butene-1-]phthalimide (II)</u>:

Under a nitrogen atmosphere, a mixture of I (28.20 g, 140 mmol), 5-bromopyrimidine (21.63 g, 136 mmol), palladium(II) acetate (306 mg, 1.4 mmol), tri-<u>o</u>-tolylphosphine (828 mg, 2.7 mmol), and triethylamine (27.54 g, 272 mmol) was stirred and heated at ~ 110°C for 27 h. The precipitated brown solids were slurried in water, filtered, and dissolved in hot N,N-dimethylformamide (DMF) (75 mL). Charcoal (Darco® G-60, 1 g) was added and the mixture filtered through Celite® (1.8 g), washing the filter cake with hot DMF (10 mL). The filtrate was diluted with an equal volume of water and cooled at 5°C for 15 h. The solids were filtered, washed with water (2 x 25 mL) and dried, producing a beige, crystalline powder (28.55 g, 75.1%). Further purification, involving two recrystallizations from DMF-water (1:1), followed by two recrystallizations from toluene afforded compound II as a light beige, crystalline powder (18.94 g, 49.8%), mp 177-178.5°C.

IR (KBr): 3445 (w), 3014 (w), 2951 (w), 1768 (m, C=O), 1703 (s, C=O), 1650 (w, C=C), 1558 (m), 1433 (s), 1402 (s), 1367 (s), 1330 (m), 1057 (m), 964 (m, trans C=C), 879 (m), 721 (s, 1,2-disubst. b nz ne), 717 (w, 5-pyrimidinyl), 633 (w, 5-pyrimidinyl) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.60 (s, 2H), 7.85 (m, 2H), 7.70 (m, 2H), 6.35 (m, 2H), 3.85 (m, 2H), 2.63 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 168.26, 157.21, 154.09, 134.07, 131.97, 131.37, 130.69, 125.60, 123.33, 37.11, 32.49.

EI-MS: m/z (relative intensity) 279 ($M^{+\cdot}$, 5%), 160 (100%), 131 (43%), 119 (45%), 104 (17%), 77 (31%), 65 (13%), 51 (11%).

HRMS: Calcd. for $C_{16}H_{13}N_3O_2$ ($M^{+\cdot}$): m/z 279.0992. Found: 279.1008.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.68; H, 4.82; N, 14.94.

<u>(E)-4-(5-Pyrimidinyl)-3-butene-1-amine (III)</u>:

Hydrazine hydrate (2.69 g, 53.7 mmol, 99%) was added to a mixture of II (6.00 g, 21.5 mmol) and methanol (100 mL), and the mixture was stirred at ambient temperature for 27 h. The white suspension was diluted with 1M NaOH solution (400 mL) and extracted with chloroform (5 x 100 mL). The chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was vacuum dried 5 h at 55°C to give (E)-4-(5-pyrimidinyl)-3-butene-1-amine (III) as a light yellow oil (2.95 g, 92.2%), which was used without further purification.

IR (film): 3345 (br, N-H), 1655 (m, C=C), 1560 (s), 1490 (s), 1440 (s), 1415 (s), 1390 (m), 1317 (s), 1190 (m), 968 (m, trans C=C), 721 (s, 5-pyrimidinyl), 636 (m, 5-pyrimidinyl) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.13 (s, 1H), 8.68 (s, 2H), 6.38 (m, 2H), 2.84 (t, 2H, J = 7 Hz), 2.40 (m, 2H), 1.26 (br s, 2H).

^{13}C NMR ($CDCl_3$): δ 157.04, 153.96, 133.16, 130.92, 124.82, 41.36, 37.44.

EI-MS: m/z (relative intensity) 148 ($M^{+\cdot}$-1, 0.1%), 132 (1%), 120 (100%), 93 (31%), 66 (40%), 51 (11%), 44 (14%).

The monofumarate of III was prepared by adding a warm solution of fumaric acid (156 mg, 1.34 mmol) in ethanol (5 mL) to a warm solution of III (100 mg, 0.67 mmol) in ethanol (3 mL). The mixture was concentrated by rotary evaporation, and the slightly yellow solids were recrystallized from ethanol-ether (1:1). The solids were filtered, washed with ethanol, ether, and vacuum dried at 50°C for 24 h, affording the monofumarate as a white, crystalline powder (63.8 mg, 35.9%), mp 160-161.5°C.

IR (KBr): 3300-2300 (br, s, amine-carboxylate), 1705 (s, C=O), 1664 (s), 1606 (s, C=C), 1556 (s), 1409 (s, fumarate), 1254 (m), 1186 (m), 981 (m, trans C=C), 852 (m), 796 (m), 723 (w, 5-pyrimidinyl), 648 (m, fumarate), 631 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR (D_2O): δ 9.00 (s, 1H), 8.84 (s, 2H), 6.69 (s, 2H), 6.63 (d, 1H, J = 16.4 Hz), 6.52 and 6.46, (dt, 1H, J = 16.1, 6.8 Hz), 3.20 (m, 2H), 2.72 (m, 2H).

^{13}C NMR (D_2O): δ 171.45, 154.10, 134.63, 131.04, 130.23, 126.05, 38.40, 30.33.

Anal. Calcd. for $C_8H_{11}N_3 \cdot C_4H_4O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.24; H, 5.75; N, 15.65.

Sample No. 2 is (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine (compound VI), which was prepared essentially in accordance with the following techniques.

<u>(E)-N-tert-Butyloxycarbonyl-4-(5-pyrimidinyl)-3-butene-1-amine (IV)</u>:

A solution of di-<u>tert</u>-butyl dicarbonate (2.66 g, 12.2 mmol) in methylene chloride (10 mL) was added dropwise over 5 min to a stirring solution of (E)-4-(5-

pyrimidinyl)-3-butene-1-amine (III) (1.70 g, 11.4 mmol) in methylene chloride at 0°C. The yellow solution was stirred at 0°C for 15 min and at ambient temperature for 22 h. Concentration by rotary evaporation, followed by vacuum drying at 30°C for 15 h afforded a yellow oil. The oil was chromatographed on silica gel (165 g), eluting first with ethyl acetate to remove impurities. Elution with chloroform-methanol (2:1) afforded the product which was re-chromatographed eluting with ethyl acetate. Selected fractions were combined in chloroform and concentrated by rotary evaporation. The residue was vacuum dried at 35°C for 48 h to give compound IV as a light yellow oil (2.56 g, 90.1%), which crystallized upon cooling, affording a light yellow, crystalline solid, mp 54-55.5°C.

IR (KBr): 3030 (w), 2990 (w), 2980 (w), 2965 (w), 2935 (w), 3298 (s, amide N-H), 1712 (s, carbamate C=O), 1657 (w, C=C), 1560 (s), 1535 (s, amide N-H), 1433 (s), 1414 (s), 1367 (s, tert-butyl), 1275 (s, amide N-H), 1246 (s, ester C-O), 1174 (s, ester C-O), 1149 (s), 1111 (m), 987 (m), 966 (m trans C=C), 723 (w, 5-pyrimidinyl), 636 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.05 (s, 1H), 8.70 (s, 2H), 6.37 (m, 2H), 4.59 (br s, 1H), 3.30 (m, 2H), 2.43 (m, 2H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 157.34, 156.83, 155.84, 154.18, 153.79, 132.24, 130.75, 125.15, 79.42, 39.64, 34.05, 28.56, 28.20.

EI-MS: m/z (relative intensity) 249 ($M^{+\cdot}$, 0.1%), 193 (15%), 176 (24%), 132 (16%), 120 (79%), 119 (85%), 93 (19%), 65 (24%), 57 (100%).

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.61; H, 7.62; N, 16.78.

<u>(E)-N-Methyl-N-tert-Butyloxycarbonyl-4-(5-pyrimidinyl)-3-butene-1-amine (V)</u>:

Under a nitrogen atmosphere, sodium hydride (0.78 g, 19.5 mmol, 60% dispersion in oil) was added to a stirring solution of IV (0.50 g, 2.0 mmol), 1,2-dimethoxyethane (20 mL), DMF (25 mL), and a trace of diisopropylamine. The mixture was stirred at ambient temperature for 45 min, and a solution of iodomethane (2.59 g, 18.3 mmol) in 1,2-dimethoxyethane (5 mL) was added. The mixture was stirred at ambient temperature for 3 days, cooled, and water (25 mL) was added dropwise. The mixture was diluted with water (200 mL) and extracted with chloroform (7 x 50 mL). All chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was dried under high vacuum at ambient temperature to give a red-brown oil. The oil was chromatographed on silica gel (50 g), eluting with ethyl acetate. Selected fractions were combined, concentrated by rotary evaporation, and dried under high vacuum at ambient temperature to give compound V as a light yellow oil (0.40 g, 76.1%).

IR (film): 3650-3200 (br, w), 2980 (m), 2940 (m), 1697 (s, carbamate C=O), 1556 (s), 1484 (s), 1452 (s), 1420 (s, N-CH_3), 1411 (s, tert-butyl), 1394 (s, tert-butyl), 1369 (s), 1304 (m), 1249 (m, ester C-O), 1218 (m), 1163 (s, ester C-O), 1136 (s), 972 (m, trans C=C), 883 (m), 774 (m), 721 (m, 5-pyrimidinyl), 631 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.63 (s, 2H), 6.31 (m, 2H), 3.32 (m, 2H), 2.82 (s, 3H), 2.44 (m, 2H), 1.39 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 157.06, 155.70, 153.95, 132.49, 130.94, 124.73, 79.51, 34.38, 28.45.

EI-MS: m/z (relative int nsity) 263 (M^+, 0.3%), 207 (5%), 190 (7%), 144 (24%), 133 (9%), 120

(39%), 93 (13%), 88 (15%), 65 (11%), 57 (100%), 44 (89%).

HRMS: Calcd. for $C_{14}H_{21}N_3O_2$ ($M^{+\cdot}$): m/z 263.1634. Found: 263.1643.

<u>(E)-N-Methyl-4-(5-pyrimidinyl)-3-butene-1-amine (VI)</u>:

Under a nitrogen atmosphere, iodotrimethylsilane (0.50 g, 2.5 mmol) was added dropwise, at ambient temperature, to a stirring solution of V (0.33 g, 1.2 mmol) in chloroform (20 mL). The red-brown mixture was stirred 30 min and methanol (20 mL) was added. The mixture was stirred 1 h and concentrated by rotary evaporation. The residue was basified with 1M NaOH solution (25 mL) and extracted with chloroform (7 x 25 mL). The chloroform extracts were combined, dried (Na_2SO_4) and concentrated by rotary evaporation, affording a brown oil. The oil was chromatographed on silica gel (35 g), eluting with methanol-ammonium hydroxide (10:1). Selected fractions were combined, vacuum dried at 45°C for 3 h, affording (E)-N-methyl-N-4-(5-pyrimidinyl)-3-butene-1-amine (VI) as a brownish-yellow oil (0.12 g, 59.6%).

IR (film): 3148 (br, s, N-H), 1653 (s, C=C), 1560 (s), 1473 (m), 1435 (s), 1414 (s, N-CH_3), 970 (m, trans C=C), 721 (s, 5-pyrimidinyl), 636 (s, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.02 (s, 1H), 8.68 (s, 2H), 6.37 (m, 2H), 2.76 (t, 2H, J = 6.8 Hz), 2.46 (m, 5H, including a N-CH_3 singlet), 1.65 (br s, 1H).

^{13}C NMR ($CDCl_3$): δ 157.09, 154.01, 132.99, 130.90, 124.81, 50.76, 36.06, 33.35.

EI-MS: m/z (relative intensity) 146 (0.3%), 132 (0.4%), 120 (22%), 93 (4%), 65 (4%), 44 (100%).

HRMS: Calcd. for C[illegible]H[illegible]N[illegible] (M^+-44): m/z 120.0676. Found: 120.0687.

Sample No. 3 is (E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine monofumarate (compound IX monofumarate), which was prepared essentially in accordance with the following techniques.

<u>3-Bromo-5-methoxypyridine (VII)</u>

This compound was prepared essentially in accordance with the techniques described in Comins et al., <u>J. Org. Chem.</u>, Vol. 55, pp. 69-73 (1990).

<u>(E)-N-4-[3-(5-methoxypyridin)yl]-3-butene-1-phthalimide (VIII)</u>:

Under a nitrogen atmosphere, a mixture of N-3-butene-1-phthalimide (I) (5.51 g, 27.4 mmol), 3-bromo-5-methoxypyridine (VII) (5.00 g, 26.6 mmol), palladium(II) acetate (59.7 mg, 0.27 mmol), tri-<u>o</u>-tolylphosphine (162 mg, 0.53 mmol), and triethylamine (5.38 g, 53.2 mmol) was stirred and heated at ~ 100°C for 21 h. The precipitated brown solids were slurried in water, filtered, and dissolved in hot DMF (30 mL). The mixture was filtered through Celite® (1 g), washing the filter cake with hot DMF (10 mL). The filtrate was diluted with an equal volume of water and cooled at 5°C for 15 h. The solids were filtered, washed with water (2 x 10 mL), cold ethanol (10 mL), and dried, producing a beige, crystalline powder (7.79 g, 95.0%). Further purification, involving two recrystallizations from DMF-water (1:1) afforded compound VIII as a light beige, crystalline powder (5.36 g, 65.4%), mp 148-151°C. An analytical sample was recrystallized from toluene, affording a light beige, crystalline powder, mp 148-151.5°C.

IR (KBr): 3440 (w), 3040 (m), 2960 (s), 2940 (s), 2825 (w), 1766 (m, C=O), 1700 (s, C=O), 1654 (m, C=C), 1580 (m, pyridinyl), 1455 (s), 1420 (s), 1320 (m), 1190 (m), 1000 (s), 973 (s, trans C=C), 867 (s,

3,5-disubst. pyridine), 723 (s, 1,2-disubst. benzene), 703 (s, 3,5-disubst. pyridine) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8.14 (s, 1H), 8.08 (s, 1H), 7.82 (m, 2H), 7.69 (m, 2H), 7.10 (dd, 1H, J = 2.4, 2.0 Hz), 6.38 (d, 1H, J = 16.1 Hz), 6.25 and 6.20 (dt, 1H, J = 15.9, 6.8 Hz), 3.84 (t, 5H, including an $O-CH_3$ singlet, J = 7.1 Hz), 2.62 (dq, 2H, J = 7.1, 1.0 Hz).

^{13}C NMR ($CDCl_3$): δ 168.27, 155.73, 140.72, 136.45, 133.96, 132.05, 129.00, 123.26, 116.80, 55.52, 37.34, 32.30.

EI-MS: m/z (relative intensity) 308 ($M^{+\cdot}$, 13%), 160 (100%), 148 (8%), 133 (10%), 105(8%), 77 (15%).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.34; H, 5.29; N, 9.00.

<u>(E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine (IX)</u>:

Hydrazine hydrate (245 mg, 4.90 mmol, 99%) was added to a mixture of VIII (500 mg, 1.62 mmol) and methanol (20 mL), and the mixture was stirred at ambient temperature for 20 h. The gray suspension was diluted with 1M NaOH solution (190 mL) and extracted with chloroform (5 x 25 mL). The chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude product (287 mg) was further purified by vacuum distillation, affording compound IX (183 mg, 62.3%) as a light yellow oil, bp 110°C at 0.05 mm Hg.

IR (film): 3350 (br, s), 3035 (s), 2940 (s), 2840 (m), 1585 (s), 1460 (s), 1425 (s), 1320 (s), 1295 (s, $ArO-CH_3$), 1185 (m), 1160 (m), 1050 (m), 1020 (sh), 965 (s, trans C=C), 885 (m, 3,5-disubst. pyridine), 820 (w), 710 (m, 3,5-disubst. pyridine).

^1H NMR ($CDCl_3$): δ 8.16 (d, 1H, J = 2.0 Hz), 8.13 (d, 1H, J = 2.9 Hz), 7.14 (dd, 1H, J = 2.6, 2.0 Hz), 6.41 (d, 1H, J = 15.9 Hz), 6.27 and 6.22 (dt, 1H,

J = 15.9, 7.1 Hz), 3.84 (s, 3H), 2.84 (t, 2H, J = 6.6 Hz), 2.36 (dq, 2H, J = 6.6, 1.0 Hz).

^{13}C NMR ($CDCl_3$): 155.79, 140.70, 136.24, 133.72, 130.79, 128.27, 116.91, 55.57, 37.29, 29.70.

EI-MS: m/z (relative intensity) 178 ($M^{+\cdot}$, 0.4%), 149 (88%), 148 (100%), 133 (12%), 105 (9%), 78 (10%).

The monofumarate of IX was prepared by adding a warm solution of fumaric acid (131 mg, 1.12 mmol) in 2-propanol (15 mL) to compound IX (166 mg, 0.93 mmol). After stirring 30 min, the solution was concentrated by rotary evaporation to a white powder. The crude product was recrystallized from 2-propanol, and the mixture was stored at ambient temperature for 15 h. The solids were filtered, washed with cold 2-propanol, ether, and vacuum dried at 50°C for 6 h, affording the monofumarate as a white, crystalline powder (177 mg, 64.6%), mp 151-153°C.

IR (KBr): 3300-2400 (br, s, amine-carboxylate), 1700 (s, C=O), 1630 (s, C=O), 1570 (sh), 1535 (m), 1460 (m), 1435 (m), 1290 (s, ArO-CH_3), 1158 (m), 1040 (m), 982 (s, trans C=C), 875 (m, 3,5-disubst. pyridine), 793 (m), 705 (m, 3,5-disubst. pyridine), 652 (m).

^1H NMR (D_2O): δ 8.31 (s, 1H), 8.25 (s, 1H), 7.85 (s, 1H), 6.68 (d, 1H, J = 16.1 Hz), 6.57 (s, 2H), 6.53 and 6.48 (dt, 1H, J = 15.9, 7.1 Hz), 3.98 (s, 3H), 3.21 (t, 2H, J = 7.1 Hz), 2.68 (q, 2H, J = 7.1 Hz).

^{13}C NMR (D_2O): δ 172.93, 156.77, 136.17, 135.62, 134.90, 131.81, 130.25, 128.04, 122.44, 56.31, 38.54, 30.14.

Anal. Calcd. for $C_{10}H_{14}N_2O \cdot C_4H_4O_4$: C, 57.14; H, 6.16; N, 9.52. Found: C, 56.91; H, 6.18; N, 9.51.

Sample No. 4 is N-Methyl-4-(3-pyridinyl)-3-butyne-1-amine which was prepared ssentially in accordance with the following techniques.

1,1-Dibromo-2-(3-pyridinyl)-ethylene (X)

Tetrabromomethane (24.82 g, 0.747 mole) and triphenylphosphine (39.17 g, 0.149 mole) were stirred together in dry methylene chloride (100 mL) for 5 min. at 0°C under a nitrogen atmosphere. To this mixture was added dropwise pyridine 3-carboxaldehyde (4 g, 0.0373 mole). The solution was then stirred for 45 min. at ambient temperature. The reaction mixture was extracted with aqueous 6N hydrochloric acid (3 x 25 mL), the aqueous layer basified with solid sodium bicarbonate to pH 8-9 and extracted with chloroform (4 x 25 mL). The combined organic liquours were dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator to give a dark colored syrup. The crude product was chromatographed on silica gel (70-230 mesh) with chloroform:methanol (95:5) as eluant, to afford a light yellow solid (5.0 g, 70%) which rapidly turned dark on standing.

^{1}H NMR($CDCl_3$) δ 8.65 (s, H), 8.58 (d, 1H), 8.00 (d, 1H), 7.45 (s, 1H), 7.22-7.36 (m, 1H).

Anal. calcd. for $C_7H_4NBr_2$: C, 31.94; H, 1.90; N, 5.32; Br, 60.84. Found: C, 32.11; H, 2.03; N, 5.50; Br, 60.99.

4-(3-Pyridinyl)-3-butyne-1-ol (XI)

To dry THF (10 mL) contained in a 50 mL round-bottomed flask fixed with a nitrogen gas balloon was added X (2.5 g, 0.01 mole). The flask was cooled to -78°C in an acetone-dry ice bath, and n-butyl lithium in THF (22 mL of a 2.5 molar solution in THF) was added dropwise via a syringe during constant stirring. After addition, the solution was stirred for 1 hour. The reaction mixture temperature was then adjusted to -60°C and ethylene oxide (1 mL) was added in one portion, and the reaction was allowed to warm to ambient temperature with stirring. Th resulting reaction mixture was quenched with water (10 mL) and

extracted with chloroform (3 x 25 mL), the combined organic liquors dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator under reduced pressure. The resulting oil was chromatographed on silica gel to afford the product as a light brown liquid (590 mg, 40%).

^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.49 (d, 1H), 7.68 (d, 1H) 7.29-7.36 (m, 1H), 3.92 (t, 2H), 2.80(m, 5H).

Anal. calcd. for C_9H_9NO: C, 73.46; H, 6.12; N, 9.52. Found: C, 73.61; H, 6.31; N, 9.66.

<u>Methanesulfonate ester of 4-(3-Pyridinyl)-3-butyne-1-ol (XII)</u>

In dry methylene chloride (2 mL) was dissolved XI (0.15 g, 1.0 mmole), and to this solution was added triethylamine (0.184 ml, 1.3 mmole). The reaction was stirred overnight under nitrogen atmosphere. The mixture was cooled to 4°C and methane sulfonyl chloride (0.15 g, 1.3 mmole) was added. The reaction mixture was then poured over ice/water (10 mL) and the resulting mixture stirred for 5 min. To this mixture was added saturated aqueous sodium bicarbonate solution (5 mL) chilled to 4°C, and the mixture stirred for 30 min., then extracted with chloroform (4 x 10 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and the volume concentrated on a rotary evaporator. The product was further purified using gel chromatography, eluting with a chloroform: methanol mixture containing 1% triethylamine. Yield of XII is 0.218 g (about 97%).

^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 7.62 (d, 1H), 7.18-7.22 (m, 1H), 4.31 (t, 2H), 3.00 (s, 3H), 2.80 (t, 2H).

N-Methyl-4-(3-pyridinyl)-3-butyne-1-amine (XIII)

An aqueous methylamine solution (5mL, 40%, 58.7 mmole) was mixed with XII (200 mg, 0.08 mmole) and stirred for 3 hr. in a sealed tube at 45°C. After the reaction was complete, water (10 mL) was added to the cooled reaction mixture, and the reaction mixture was extracted with chloroform (10 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was chromatographed on a silica gel column using methanol:chloroform (1:9) and then with a chloroform: methanol mixture containing 1% triethylamine as eluent. About 70 mg of XIII was obtained as a slightly yellow syrup, which was distilled at 110-112°C, 0.04 mm Hg. XIII was converted to its mono fumarate salt form, which exhibits a melting point of 103-104°C.

Free base. ^1H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.48 (d, 1H), 7.62 (d, 1H), 7.20 (t, 1H), 2.82 (t, 2H), 2.61 (t, 2H), 2.33 (s, 3H), 1.4 (br s, 1H).

Fumarate salt. ^1H NMR (D_2O) δ 8.51 (s, 1H), 8.89 (d, 1H), 7.91 (d, 1H), 7.40 (m, 1H), 6.28 (s, 2H), 3.20 (t, 2H), 2.80 (t, 2H), 2.62 (s, 3H).

^{13}C NMR (D_2O) δ 164.5, 151.8, 148.0, 146.0, 138.8, 128.2, 124.5, 93.0, 82.3, 50.4, 36.2, 20.1.

Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.70; N, 10.14. Found: C, 60.84; H, 5.72; N, 10.23.

Sample No. 5 is (Z)-metanicotine which was prepared essentially in accordance with the following techniques.

(Z)-Metanicotine (XIV)

Into a hydrogenation bottle together with methanol (20 mL), glacial acetic acid (1 mL) and a catalytic amount of quinolin was placed XIII fre base (200 mg, 1.25 mmole). Lindlar's catalyst (palladium/calcium carbonat poisoned with lead) (60

mg) was added and the mixture hydrogenated at 50 psig in a Parr reaction apparatus overnight at ambient temperature. The catalyst was filtered off, the resulting solution basified with aqueous sodium hydroxide (50% w/v) to a pH 8-9, and then extracted with chloroform (3 x 25 mL). The combined organic liquors were concentrated on a rotary evaporator, and the residue chromatographed on 60-230 mesh silica gel, using chloroform:methanol: triethylamine (90:10:1) as eluent, to afford XIV as a colorless oil at about 100% yield. XIV is converted to its mono fumarate salt, which has a melting point of 117-118°C.

Free-base, ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.42 (d, 1H), 7.60 (d, 1H), 7.22 (m, 1H), 6.81 (m, 1H), 6.51 (d, 1H), 2.79 (t, 2H), 2.52 (m, 2H), 2.41 (s, 3H).

Difumarate salt. ^{1}H NMR (D_2O) δ 8.48 (br s, 2H), 8.10 (d, 1H), 7.75-7.63 (m, 1H), 6.52 (d, 1H), 6.40 (s, 1H), 5.85-5.78 (m, 1H), 3.00 (t, 2H), 2.51 (m, 5H).

Anal. calcd. for $C_{10}H_{14}N_2.2C_4H_4O_4$: C, 54.82; H, 5.58; N, 7.10. Found: C, 54.47; H, 5.68; N, 6.98.

Sample No. 6 is (E)-N-methyl-4-[3-(6-methylpyrindin)yl]-3-butene-1-amine which was prepared essentially in accordance with the following techniques.

<u>6-Methylmyosmine (XV)</u>

Sodium hydride (60% in oil) (1.9 g, 0.079 mole) was placed in a 250 mL two-necked round bottom flask and washed with dry THF (50 mL). A further aliquot of dry THF (100 mL) was added followed by a solution of N-vinylpyrrolidone (4.7 g, 0.04 mole) in dry THF (30 mL), and the mixture stirred for 30 min. at ambient temperature. A solution of ethyl 6-methylnicotinate (5.0 g, 0.033 mol) in dry THF (20 mL) was then added dropwise over 10 min., during which time

evolution of hydrogen occurred. The reaction was flushed with nitrogen, and the mixture refluxed for 6 hr. After cooling, aqueous hydrochloric acid (6N, 25 mL) was added and the THF removed by rotory evaporation under reduced pressure. A further volume of aqueous hydrochloric acid (6N, 20 mL) was added and the mixture refluxed overnight. On cooling, the mixture was basified with aqueous sodium hydroxide (50% w/v) to pH 8-9, and XV was extracted with chloroform (5 x 20 mL). The combined organic liquours were dried over anhydrous sodium sulfate, filtered and the solvent evaporated to afford XV, which was crystallized from methanol as a tan solid (4.45 g, 84%).

^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.15 (d, 1H), 7.20 (d, 1H), 4.12 (t, 2H), 2.98 (t, 2H), 2.80 (s, 3H), 2.00 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 172.5, 160.08, 148.1, 135.01, 122.7, 61.5, 34.8, 24.2, 22.2.

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.00, H, 7.50; N, 17.50. Found: C, 74.94; H, 7.51; N, 17.47.

(+/-)-6-Methylnornicotine (XVI)

Into a round bottom flask was placed XV (3.0 g, 0.018 mole), methanol (20 mL) and glacial acetic acid (4 mL). The mixture was cooled to -78°C in a dry ice-acetone bath, and sodium borohydride (1.332 g, 0.36 mole) was added over 30 min. After addition, the reaction mixture was allowed to warm to ambient temperature, and stirred for 1 hr. The methanol then was removed on a rotary evaporator under reduced pressure and the residue was basified with aqueous sodium hydroxide (50% w/v) to pH 8-9. The aqueous solution was extracted with chloroform (5 x 25 mL) and the combined organic liquors dried over anhydrous sodium sulfate, filtered and evaporated on a rotary evaporator to afford XVI as a dark brown liquid, which

was distilled at 4 mm Hg to yield a clear, colorless liquid (b.p. is 113-114°C, 4mm Hg) (2.43 g, 80%).

^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 7.60 (d, 1H), 7.10 (d, 1H), 4.15 (t, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.30 (s, 3H), 2.20-2..00 (m, 3H), 2.00-1.98 (m, 2H), 1.78-1.60 (m, 2H).

$HClO_4$ salt ^{1}H NMR (D_2O) δ 8.62 (s, 1H), 8.40 (d, 1H), 7.81 (d, 1H), 3.58 (t, 2H), 2.78 (s, 3H), 2.40-2.20 (m, 4H).

Anal. calcd. for $C_{10}H_{16}N_2Cl_2O_8$: C, 33.05; H, 4.40; N, 7.71; Cl, 19.55. Found: C, 33.16; H, 4.46; N, 7.64; Cl, 19.43.

<u>(+/-)-6-Methylnicotine (XVII)</u>

Into a round bottom flask was placed XVI (2.0 g), and formaldehyde (37% w/v in water, 20 mL) and formic acid (95-97% w/v, 45 mL), both a 0°C, were added. The mixture then was refluxed under nitrogen for 8 hr. The cooled reaction mixture was basified with aqueous sodium hydroxide (50% w.v) to pH 8-9, and the solution extracted with chloroform (5 x 25 mL). The combined organic liquors were dried over anhydrous sodium sulfate, filtered and evaporated; and the resulting oil distilled under reduced pressure to afford XVII as a clear, odorless oil (b.p. 107°C at 3 mm Hg, 92% yield).

^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.60 (d, 1H), 7.12 (d, 1H), 3.15 (t, 1H), 3.00 (t, 1H), 2.56 (s, 3H), 2.40-2.20 (m, 1H), 2.18-2.08 (m, 4H), 2.00 - 1.92 (m, 1H), 1.80-1.60 (m, 2H).

$HClO_4$ salt. Anal. calcd. for $C_{11}H_{18}N_2Cl_2O_8$: C, 35.01; H, 4.77; N, 7.42; Cl, 18.83. Found: C, 35.12; H, 4.85; N, 7.37; Cl, 18.76.

<u>N-Ethylcarbamate of (+/-)-6-methylmetanicotine (XVIII)</u>

To a stirred solution of XVII (3.0 g, 0.017 mole) in methylene chloride (25 mL) under nitrogen

atmosph re was added dropwis a solution of ethylchloroformate (2.40 g) in methylene chloride (10 mL) at ambient temperature. The mixture was refluxed for 4 hr. After evaporation of solvent on a rotary evaporator under reduced pressure, the resulting oil was vacuum distilled to give XVIII as a thick viscous liquid (b.p. 172-175°C, 4 mm Hg), which was further purified by silica column chromatography, to yield about 3 g of XVIII (70% yield).

^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.61 (d, 1H), 7.08 (d, 1H), 6.60 (d, 1H), 6.08-6.00 (m, 1H), 4.18 (q, 2H), 3.40 (m, 2H), 2.91 (s, 3H), 2.60-2.42 (m, 5H), 1.22 (t, 3H).

<u>(E)-N-methyl-4-[3-(6-methylpyrindin)yl]-3-butene-1-amine (XIX)</u>

Into a round bottom flask was placed XVIII (3.0 g, 0.012 mole), and concentrated hydrochloric acid (15 mL) was added. The mixture was refluxed overnight, and the resulting solution basified with aqueous sodium hydroxide (50% w/v) to pH 8-9. The solution was extracted with chloroform (4 x 25 mL), the combined organic liquors dried over anhydrous sodium carbonate, filtered, and the solvent evaporated to afford an oil. Vacuum distillation of the oil afforded XIX as a clear, colorless liquid (b.p. 80°C at 0.2 mm Hg, 78% yield). XIX then was provided in the form of a monofumarate salt, m.p. 134-135°C.

Difumarate salt. ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 7.76 (d, 1H), 7.20 (d, 1H), 6.52-6.24 (m, 4H), 3.00 (t, 2H), 2.60-2.00 (m, 3H).

Anal. Calcd. for $C_{11}H_{16}N_2.2C_4H_4O_4$: C, 55.88; H, 5.88; N, 6.86. Found: C, 55.72; H, 5.93; N, 6.83.

Sample No. 7 is N-methyl-(3-pyridinyl)-butane-1-amine, which was prepar d essentially in accordance with th following techniques.

(E)-Metanicotine (0.4 g, 2.46 mmole) was dissolved in a mixture of methanol (20 mL) and glacial acetic acid (1 mL) and 5% Pd-C catalyst (30 mg) was added. The mixture was hydrogenated at 50 psig hydrogen for 2 hr. The reaction mixture then was filtered and the solvent removed on a rotary evaporator. To the residue was added water (5 mL) and the aqueous solution basified to pH 8-9 with 40% aqueous sodium hydroxide. The mixture then was extracted with chloroform (5 x 10 mL), and the combined organic liquors dried over potassium carbonate, filtered and solvent was evaporated under reduced pressure on a rotovaporator. The resulting oil then was provided in the form of a difumarate salt, melting point being 115-116°C.

Free base. ^1H NMR ($CDCl_3$) δ 8.42 (m, 2H), 7.50 (d, 1H), 7.20 (m, 1H), 2.64-2.58 (m, 4H), 2.40 (s, 3H), 2.78-2.60 (m, 2H), 2.42-2.59 (m, 2H), 1.22 (broad s, 1H).

Difumarate salt. ^1H NMR (D_2O) δ 8.64 (d, 2H), 8.43 (d, 1H), 8.00 (m, 1H), 6.62 (s, 4H), 3.24 (t, 2H), 2.90 (t, 2H), 2.70 (s, 3H), 1.81-1.69 (m, 4H).

Anal. calcd. for $C_{10}H_{16}N_2.2C_4H_4O_4.1/2H_2O$: C, 53.33; H, 6.17; N, 6.91. Found: C, 53.33; H, 6.06; N, 7.07.

Sample No. 8 is (E)-metanicotine which was provided generally using the techniques set forth by Laforge, J.A.C.S., Vol. 50, p. 2477 (1928).

For comparison purposes, Sample No. C-1 was provided. This sample is (S)-(-)-nicotine, which has been reported to have demonstrated a positive effect towards the treatment of various CNS disorders.

Determination of binding of compounds to relevant receptor sites

Rats (Sprague-Dawley) were maintained on a 12 hour light/dark cycle and were allowed free access to water and food supplied by Wayne Lab Blox, Madison, WI. Animals used in the present studies weighed 200 to 250 g. Brain membrane preparations were obtained from brain tissue of either males or females.

Rats were killed by decapitation following anesthesia with 70% CO_2. Brains were removed and placed on an ice-cold platform. The cerebellum was removed and the remaining tissue was placed in 10 volumes (weight:volume) of ice-cold buffer (Krebs-Ringers HEPES: NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 2.5 mM; $MgSO_4$, 1.2 mM; HEPES, 20 mM; pH to 7.5 with NaOH) and homogenized with a glass-Teflon tissue grinder. The resulting homogenate was centrifuged at 18,000 x g for 20 min. and the resulting pellet was resuspended in 20 volumes of water. After 60 min. incubation at 4°C, a new pellet was collected by centrifugation at 18,000 x g for 20 min. After resuspension in 10 volumes of buffer, a new final pellet was again collected by centrifugation at 18,000 x g for 20 min. Prior to each centrifugation step, the suspension was incubated at 37°C for 5 min. to promote hydrolysis of endogenous acetylcholine. The final pellet was overlayered with buffer and stored at -70°C. On the day of the assay, that pellet was thawed, resuspended in buffer and centrifuged at 18,000 x g for 20 min. The pellet obtained was resuspended in buffer to a final concentration of approximately 5 mg protein/ml. Protein was determined by the method of Lowry et al., J. Biol. Chem., Vol. 193, pp. 265-275 (1951), using bovin serum albumin as the standard.

The binding of L-[^{3}H]nicotin was measured using a modificati n of th m thod of Romano et al., Science, Vol. 210, pp. 647-650 (1980) as d scribed

previously by Marks et al., <u>Mol. Pharmacol.</u>, Vol. 30, pp. 427-436 (1986). The L-[^{3}H]nicotine used in all experiments was purified chromatographically by the method of Romm, et al., <u>Life Sci.</u>, Vol. 46, pp. 935-943 (1990). The binding of L-[^{3}H]nicotine was measured using a 2 hr. incubation at 4°C. Incubations contained about 500 ug of protein and were conducted in 12 mm x 75 mm polypropylene test tubes in a final incubation volume of 250 ul. The incubation buffer was Krebs-Ringers HEPES containing 200 mM TRIS buffer, Ph 7.5. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (Micro Filtration Systems) that had been soaked in buffer containing 0.5 percent polyethyleneimine. Filtration vacuum was -50 to -100 torr. Each filter was washed five times with 3 ml of ice-cold buffer. The filtration apparatus was cooled to 2°C before use and was kept cold through the filtration process. Nonspecific binding was determined by inclusion of 10 uM nonradioactive nicotine in the incubations.

The inhibition of L-[^{3}H]nicotine binding by test compounds was determined by including one of eight different concentrations of the test compound in the incubation. Inhibition profiles were measured using 10 nM L-[^{3}H]nicotine and IC_{50} values were estimated as the concentration of compound that inhibited 50 percent of specific L-[^{3}H]nicotine binding. Inhibition constants (Ki values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., <u>Biochem. Pharmacol.</u>, Vol. 22, pp. 3099-3108 (1973).

<u>Determination of Dopamine Release</u>

Dopamine release was measured by preparing synaptosomes from the striatal area of rat brain obtained from Sprague-Dawley rats generally according to the procedures set forth by Nagy et al., <u>J. Neurochem.</u>, Vol. 43, pp. 1114-1123 (1984). Striata

from 4 rats w re homogeniz d in 2 ml of 0.32M sucros buffered with 5 mM HEPES (pH 7.5), using a glass-Teflon tissue grinder. The homogenate was diluted to 5 ml with additional homogenization solution and centrifuged at 1,000 x g for 10 min. This procedure was repeated on the new pellet and the resulting supernatant was centrifuged at 12,000 x g for 20 min. A 3 layer discontinuous Percoll gradient consisting of 16 percent, 10 percent and 7.5 percent Percoll in HEPES-buffered sucrose was made with the final pellet dispersed in the top layer. After centrifugation at 15,000 x g for 20 min., the synaptosomes were recovered above the 16 percent layer with a Pasteur pipette, diluted with 8 ml of perfusion buffer (128 mM NaCl, 2.4 mM KCl, 3.2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25 mM HEPES pH 7.4, 10 mM dextrose, 1 mM ascorbate, 0.01 Mm pargyline), and centrifuged at 15,000 x g for 20 min. The new pellet was collected and re-suspended in perfusion buffer. The synaptosome suspension was incubated for 10 min. at 37°C. [^{3}H]-Dopamine (Amersham, 40-60 Ci/mmol) was added to the suspension to give a final concentration of 0.1 uM, and the suspension was incubated for another 5 min. Using this method, 30 to 90 percent of the dopamine was taken up into the synaptosomes, as determined by scintillation counting following filtration through glass fiber filters soaked with 0.5 percent polyethyleneimine. A continuous perfusion system was used to monitor release following exposure to each ligand. Synaptosomes were loaded onto glass fiber filters (Gelman type A/E). Perfusion buffer was dripped onto the filters (0.2-0.3 ml/min.) and pulled through the filters with a peristaltic pump. Synaptosomes were washed with perfusion buffer for a minimum of 20 min. before addition of the ligand. After the addition of 0.2 ml of a solution containing various concentrations of ligand, the perfusate was collect d into scintillation vials at 1 min. intervals

and the dopamine released was quantified by scintillation counting. Peaks of radioactivity released above background were summed and the average basal release during that time was subtracted from the total. Release was expressed as a percentage of release obtained with an equal concentration of (S)-(-)-nicotine.

Determination of Log P

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968)), were calculated according to the methods described by Hopfinger, Conformational Properties of Macromolecules, Academic Press (1973) using Cerius^2 software package by Molecular Simulations, Inc. for Sample Nos. 1-3, 5-8 and C-1, and Bodor, University of Florida (1991) using the BLogP software package by CAChe Scientific, Inc. for Sample No. 4.

Determination of Interaction with Muscle

Human muscle activation was established on the human clonal line TE671/RD which is derived from an embryonal rhabdomyosarcoma (Stratton et al., Carcinogen, Vol. 10, pp. 899-905 (1989)). As evidenced through pharmacological (Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989)), electrophysiological (Oswald et al, Neurosci. Lett., Vol. 96, pp. 207-212 (1989)), and molecular biological studies (Luther et al., J. Neurosci., Vol. 9, pp. 1082-1096 (1989)) these cells express muscle-like nicotinic receptors. Nicotinic acetylcholine receptor (nAChR) function was assayed using ^{86}Rb efflux according to a method d scribed by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Dose-response curves were plott d and the concentration resulting in half maximal

activation of sp cific ion flux through nicotinic receptors determined for human muscle and rat ganglionic preparations (EC50). The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine.

Determination of Interaction with Ganglia

Ganglionic effects were established on the rat pheochromocytoma clonal line PC12, which is a continuous clonal cell line of neural crest origin derived from a tumor of the rat adrenal medulla expressing ganglionic-type neuronal nicotinic receptors (see Whiting et al., Nature, Vol. 327, pp. 515-518 (1987); Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989); Whiting et al., Mol. Brain Res., Vol. 10, pp. 61-70 (1990)). Discussion concerning the heterogeneity of nicotinic receptors subtypes is set forth in Lukas et al., Internatl. Review Neurobiol., Vol. 34, pp. 25-130 (1992). Acetylcholine nicotinic receptors expressed in rat ganglia share a very high degree of homology with their human counterparts. See, Fornasari et al., Neurosci. Lett., Vol. 111, pp. 351-356 (1990) and Chini et al., Proc. Natl. Acad. Sci. USA, Vol. 89, pp. 1572-1576 (1992). Both clonal cell lines described above were maintained in proliferative growth phase according to routine protocols (Bencherif et al., Mol. Cell. Neurosci., Vol. 2, pp. 52-65, (1991) and Bencherif et al., J. Pharmacol. Exp. Ther., Vol. 257, pp. 946-953 (1991)). Intact cells on dishes were used for functional studies. Routinely, sample aliquots were reserved for determination of protein concentration using the method of Bradford, Anal. Biochem., Vol. 72, pp. 248-254 (1976) with bovine serum albumin as the standard.

Nicotinic acetylcholin receptor (nAChR) function was assayed using $^{86}Rb^{+}$ efflux according to a

method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Cells were plated in 35-mm diameter wells of 6-well dishes for at least 48 hours and loaded for at least 4 hours at 37°C in a medium containing serum, and 1μCi/ml $^{86}Rb^{+}$. Following removal of the loading medium, cells were quickly washed three times with label-free Ringer's solution and exposed for 4 minutes at 20°C to 900 μl of Ringer's containing the indicated concentration of compound to be tested (to define total efflux) or in addition to 100 μM mecamylamine (to define non-specific efflux). The medium was removed and $^{86}Rb^{+}$ was quantitated using Cerenkov detection (see Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988)). Specific ion efflux was determined as the difference in isotope efflux between total and non-specific efflux samples. Dose-response curves were plotted and the concentration resulting in half maximal activation of specific ion flux through nicotinic receptors determined for human muscle and rat ganglionic preparations (EC50). The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine.

Data are presented in Table I.

Table I

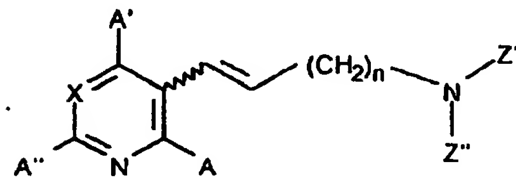
Sample No.	Ki (nM)	logP	Dopamine Release EC50 (nM)	Dopamine Release Emax (%nicotine)	Muscle Effect (% nicotine)	Ganglion Effect (% nicotine)
C-1*	2	0.71	115	100	100	100
1	269	-0.30	4360	113	0	0
2	86	0.04	5800	77	4	1
3	22	1.13	4000	95	0	0
4	58	1.82	8350	87	7	59
5	77	1.39	11339	88	0	0
6	176	1.92	219	60	2	4
7	910	1.51	ND	72	0	31
8	16	1.39	1470	80	15	0

* not an example of the invention
ND = not determined

The data in Table I indicate that the compounds have the capability of passing the blood-brain barrier by virtue of their favorable logP values, binding to high affinity CNS nicotinic receptors as indicated by their low binding constants, and activating CNS nicotinic receptors of a subject and causing neurotransmitter release, thereby demonstrating known nicotinic pharmacology. Thus, the data indicate that such compounds have the capability of being useful in treating CNS disorders involving nicotinic cholinergic systems. Furthermore, the data indicate that the compounds do not cause any appreciable effects at muscle sites and ganglionic sites, thus indicating a lack of undesirable sid effects in subjects receiving administration of those compounds.

THAT WHICH IS CLAIMED IS:

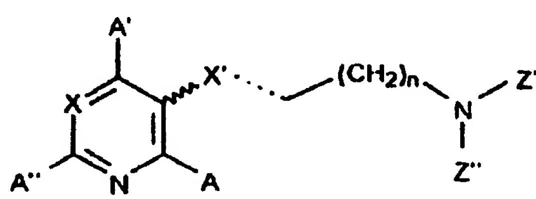
1. A compound having the formula:



wherein X is C-H; n is 2; A'' is methyl; A, A', Z' and Z'' each are hydrogen; and Z'' is hydrogen or methyl.

2. The compound of Claim 1 wherein that compound is (E)-N-methyl-4-(3-(6-methylpyrindin)yl)-3-butene-1-amine

3. A compound having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value between about -0.3 and about 0.75; n is an integer which ranges from 1 to 5; Z' and Z'' individually represent hydrogen or alkyl containing one to five carbon atoms; A and A' represent hydrogen; A'' represents hydrogen, methyl or ethyl; the dashed line in the structure represents a C-C triple bond; the wavy line in the structure repres nts C-C single bond, and X' represents C.

4. The compound of Claim 3 wh rein X is C-H; n is 2; A, A′, A′′ and Z′ each are hydrogen; and Z′′ is hydrogen or methyl.

5. The compound of Claim 3 wherein the compound is and N-methyl-4-(3-pyridinyl)-3-butyne-1-amine.

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Computer Search 1966 - To Date

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 5,212,188 (CALDWELL ET AL.) 18 May 1993, see column 6, lines 1-60.	1, 2 ------ 1, 2
X -- Y -- A	Chemical Abstracts, Volume 109, Number 25, issued 19 December 1988, KURBANOV ET AL., "Aminomethylation of 2-methyl-5-ethynyl pyridine by dimethyl- and diethyl amines", page 834, second column, Abstract 230750t, Uzb. Kim. Zh., 1988, (2), pages 31-33, see entire abstract.	3 ----- 3 ----- 4, 5
X -- Y -- A	Chemical Abstracts, Volume 71, Number 16, issued 20 October 1969, KOTLYAREVSKII ET AL., "Synthesis and some reactions of β-ethynylpyridine," page 368, first column, Abstract 81101z, Ser. Khim. Nauk, 1969, (2), pages 111-115, see entire abstract.	3 -- 3 ---- 4,5

Further documents are listed in the continuation of Box C. See patent family annex.

* [illegible]
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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract

Patients susceptible to or suffering from central nervous system disorders (e.g., Tourette's syndrome, attention deficit disorder r schizophrenia) are treated by administering an effective amount of an aryl substituted aliphatic compound, an aryl substituted olefinic amine compound or an aryl substituted acetylenic compound. Exemplary compounds are (E)-4-(5-pyrimidinyl)-3-butene-1-amine, (E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine, (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine, (E)-N-methyl-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine, (Z)-metanicotine, (E)-metanicotine, N-methyl-(3-pyridinyl)-butane-1-amine, N-methyl-4-(3-pyridinyl)-3-butyne-1-amine and (E)-N-methyl-4-[3-(6-methylpyridin)yl]-3-butene-1-amine.

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PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

BACKGROUND OF THE INVENTION

The present invention relates to compounds having pharmaceutical properties, and in particular, to compounds useful for preventing and treating central nervous system (CNS) disorders. The present invention relates to a method for treating patients suffering from or susceptible to such disorders, and in particular, to a method for treating patients suffering from those disorders which are associated with neurotransmitter system dysfunction. The present invention also relates to compositions of matter useful as pharmaceutical compositions in the prevention and treatment of CNS disorders which have been attributed to neurotransmitter system dysfunction.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia

(early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning, orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a neurotransmitter involved in learning and memory mechanisms). See, Jones, et al., Intern. J. Neurosci., Vol. 50, p. 147 (1990); Perry, Br. Med. Bull., Vol. 42, p. 63 (1986) and Sitaram, et al., Science, Vol. 201, p. 274 (1978). It has been observed that nicotinic acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. See, Giacobini, J. Neurosci. Res., Vol. 27, p. 548 (1990); and Baron, Neurology, Vol. 36, p. 1490 (1986). As such, it would seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Certain attempts have been made to treat SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such receptors upon chronic administration to animals. See, Rowell, Adv. Behav. Biol., Vol. 31, p. 191 (1987); and Marks, J. Pharmacol.

Exp. Ther., Vol. 226, p. 817 (1983). It also has been proposed that nicotine can act directly to elicit the release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. See, Rowell, et al., J. Neurochem., Vol. 43, p. 1593 (1984); Sherwood, Human Psychopharm., Vol. 8, pp. 155-184 (1993); Hodges, et al., Bio. of Nic., Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., Br. J. Psych., Vol. 154, p. 797 (1989); and U.S. Patent Nos. 4,965,074 to Leeson and 5,242,935 to Lippiello et al. Other methods for treating SDAT have been proposed, including U.S. Patent Nos. 5,212,188 to Caldwell et al. and 5,227,391 to Caldwell et al. and European Patent Application No. 588,917. Another proposed treatment for SDAT is Cognex, which is a capsule containing tacrine hydrochloride, available from Parke-Davis Division of Warner-Lambert Company, which reportedly preserves existing acetylcholine levels in patients treated therewith.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. See, Rinne, et al., Brain Res., Vol. 54, pp. 167-170 (1991) and Clark, et al., Br. J. Pharm., Vol. 85, pp. 827-835 (1985). It also has been proposed that nicotine can ameliorate the symptoms of PD. See, Smith et al., Rev. Neurosci., Vol. 3(1), pp. 25-43 (1982).

Certain attempts hav been made to treat PD. One proposed treatment for PD is Sinemet CR, which is a sustained-release tablet containing a mixture of

carbidopa and levodopa, available from The DuPont Merck Pharmaceutical Co. Another proposed treatment for PD is Eldepryl, which is a tablet containing selefiline hydrochloride, available from Somerset Pharmaceuticals, Inc. Another proposed treatment for PD is Parlodel, which is a tablet containing bromocriptine mesylate, available from Sandoz Pharmaceuticals Corporation. Another method for treating PD and a variety of other neurodegenerative diseases has been proposed in U.S. Patent No. 5,210,076 to Berliner et al.

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of neurological and behavioral symptoms. Typical symptoms include (i) the onset of the disorder before the age of 21 years, (ii) multiple motor and phonic tics although not necessarily concurrently, (iii) variance in the clinical phenomenology of the tics, and (iv) occurrence of quasi daily tics throughout a period of time exceeding a year. Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing; while phonic or vocal tics include throat clearing, sniffling, yelping, tongue clicking and uttering words out of context. The pathophysiology of TS presently is unknown, however it is believed that neurotransmission dysfunction is implicated with the disorder. See, Calderon-Gonzalez et al., Intern. Pediat., Vol. 8(2), pp. 176-188 (1993) and Oxford Textbook of Medicine, Eds. Weatherall et al., Chapter 21.218 (1987).

It has been proposed that nicotine pharmacology is beneficial in suppressing the symptoms associated with TS. See, Devor et al., The Lancet, Vol. 8670, p. 1046 (1989); Jarvik, British J. of Addiction, Vol. 86, pp. 571-575 (1991); McConville et al., Am. J. Psychiatry, Vol. 148 (6), pp. 793-794 (1991); Newhouse et al., Brit. J. Addic., Vol. 86, pp. 521-526 (1991); McConville et al., Biol. Psychiatry,

Vol. 31, pp. 832-840 (1992); and Sanberg et al., *Proceedings from Intl. Symp. Nic.*, S39 (1994). It also has been proposed to treat TS using Haldol, which is haloperidol available from McNeil Pharmaceutical; Catapres, which is clonidine available from Boehringer Ingelheim Pharmaceuticals, Inc., Orap, which is pimozide available from Gate Pharmaceuticals; Prolixin, which is fluphenazine available from Apothecon Division of Bristol-Myers Squibb Co.; and Klonopin, which is clonazepam available from Hoffmann-LaRoche Inc.

Attention deficit disorder (ADD) is a disorder which affects mainly children, although ADD can affect adolescents and adults. See, Vinson, *Arch. Fam. Med.*, Vol. 3(5), pp. 445-451 (1994); Hechtman, *J. Psychiatry Neurosci.*, Vol. 19 (3), pp. 193-201 (1994); Faraone et al., *Biol. Psychiatry*, Vol. 35(6), pp. 398-402 (1994) and Malone et al., *J. Child Neurol.*, Vol. 9(2), pp. 181-189 (1994). Subjects suffering from the disorder typically have difficulty concentrating, listening, learning and completing tasks; and are restless, fidgety, impulsive and easily distracted. Attention deficit disorder with hyperactivity (ADHD) includes the symptoms of ADD as well as a high level of activity (e.g., restlessness and movement). Attempts to treat ADD have involved administration of Dexedrine, which is a sustained release capsule containing dextroamphetamine sulfate, available from SmithKline Beecham Pharmaceuticals; Ritalin, which is a tablet containing methylphenidate hydrochloride, available from Ciba Pharmaceutical Company; and Cylert, which is a tablet containing premoline, available from Abbott Laboratories. In addition, it has been reported that administration of nicotine to an individual improves that individual's selective and sustained attention. See, Warburton et al., *Cholinergic control of cognitive resources, Neuropsychobiology*, Eds. Mendlewicz, et al., pp. 43-46 (1993).

Schizophrenia is characterized by psychotic symptoms including delusions, catatonic behavior and prominent hallucinations, and ultimately results in a profound decline in the psychosocial affect of the subject suffering therefrom. Traditionally, schizophrenia has been treated with Klonopin, which is available as a tablet containing clonezepam, available from Hoffmann-LaRoche Inc.; Thorazine, which is available as a tablet containing chlorpromazine, available from SmithKline Beecham Pharmaceuticals; and Clozaril, which is a tablet containing clozapine, available from Sandoz Pharmaceuticals. Such neuroleptics are believed to be effective as a result of interaction thereof with the dopaminergic pathways of the CNS. In addition, a dopaminergic dysfunction possessed by individuals suffering from schizophrenia has been proposed. See, Lieberman et al., Schizophr. Bull., Vol. 19, pp. 371-429 (1993) and Glassman, Amer. J. Psychiatry, Vol. 150, pp. 546-553 (1993). Nicotine has been proposed as being effective in effecting neurotransmitter dysfunction associated with schizophrenia. See, Merriam et al., Psychiatr. Annals, Vol. 23, pp. 171-178 (1993) and Adler et al., Biol. Psychiatry, Vol. 32, pp. 607-616 (1992).

Nicotine has been proposed to have a number of pharmacological effects. Certain of those effects may be related to effects upon neurotransmitter release. See, for example, Sjak-shie et al., Brain Res., Vol. 624, pp. 295-298 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported by Rowell et al., J. Neurochem., Vol. 43, pp. 1593-1598 (1984); Rapier et al., J. Neurochem., Vol. 50, pp. 1123-1130 (1988); Sandor et al., Brain Res., Vol. 567, pp. 313-316 (1991) and Vizi, Br. J. Pharmacol., Vol. 47, pp. 765-777 (1973). Release of norepinephrine by neurons

upon administration of nicotine has been reported by Hall et al., Biochem. Pharmacol., Vol. 21, pp. 1829-1838 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., Arch. Int. Pharmacodyn. Ther., Vol. 296, pp. 91-97 (1977). Release of glutamate by neurons upon administration of nicotine has been reported by Toth et al., Neurochem Res., Vol. 17, pp. 265-271 (1992). Therefore, it would be desirable to provide a pharmaceutical composition containing an active ingredient having nicotinic pharmacology, which pharmaceutical composition is capable of eliciting neurotransmitter release within a subject in order to prevent or treat a neurological disorder. In addition, nicotine reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used for the treatment of certain CNS disorders. See, Sanberg et al., Pharmacol. Biochem. & Behavior, Vol. 46, pp. 303-307 (1993); Harsing et al., J. Neurochem., Vol. 59, pp. 48-54 (1993) and Hughes, Proceedings from Intl. Symp. Nic., S40 (1994). Furthermore, various other beneficial pharmacological effects of nicotine have been proposed. See, Decina et al., Biol. Psychiatry, Vol. 28, pp. 502-508 (1990); Wagner et al., Pharmacopsychiatry, Vol. 21, pp. 301-303 (1988); Pomerleau et al., Addictive Behaviors, Vol. 9, p. 265 (1984); Onaivi et al., Life Sci., Vol. 54(3), pp. 193-202 (1994) and Hamon, Trends in Pharmacol. Res., Vol. 15, pp. 36-39.

It would be desirable to provide a useful method for the prevention and treatment of a CNS disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a disorder. It would be highly beneficial to provide individuals suffering from c rtain CNS disorders with int rruption of th symptoms of those diseases by the administration of a pharmaceutical composition which

has nicotinic pharmacology and which has a beneficial effect upon the functioning of the CNS, but which does not provide any significant associated side effects (e.g., increased heart rate and blood pressure) attendant with interaction of that compound with cardiovascular sites. It would be highly desirable to provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors which have the potential to affect the functioning of the CNS, but which does not significantly affect those receptors which have the potential to induce undesirable side effects (e.g., appreciable pressor cardiovascular effects and appreciable activity at skeletal muscle sites).

SUMMARY OF THE INVENTION

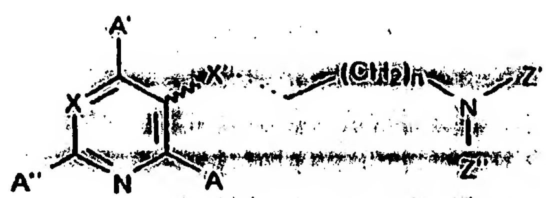
The present invention relates to aryl substituted aliphatic amine compounds, aryl substituted olefinic amine compounds and aryl substituted acetylenic amine compounds. The present invention relates to a method for providing prevention or treatment of a central nervous system (CNS) disorder. The method involves administering to a subject an effective amount of a compound of the present invention. The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a compound of the present invention. Such a pharmaceutical composition incorporates a compound which has the capability of interacting with relevant nicotinic receptor sites of a subject, and hence has the capability of acting as a therapeutic in the prevention or treatment of a CNS disorder.

Th pharmaceutical compositions of the pres nt invention are useful for the prevention and treatment of CNS disorders. The pharmaceutical compositions provide therapeutic benefit to individuals

suffering from certain CNS disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions have the potential to (i) exhibit nicotinic pharmacology and affect nicotinic receptors sites in the CNS (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) not provide appreciable adverse side effects (e.g., significant increases in blood pressure and heart rate, and significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of CNS disorders.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

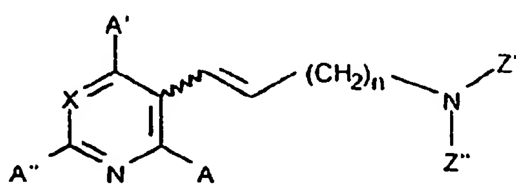
The present invention, in one aspect, relates to certain compounds having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0, as determined in accordance with Hansch et al., Chem. Rev., Vol. 91, pp. 165-195 (1991); n is an integer which can range from 1

to 5, preferably from 1 to 3, and most preferably is 2 or 3; Z' and Z'' individually represent hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, such as methyl, ethyl or isopropyl), and preferably at least one of Z' and Z'' is hydrogen; A, A' and A'' individually represent hydrogen, alkyl (e.g., lower straight chain or branched alkyl, including C_1 - C_7 , but preferably methyl or ethyl) or halo (e.g., F, Cl, Br or I); the dashed line in the structure represents a C-C single bond, a C-C double bond or a C-C triple bond; the wavy line in the structure represents a cis (Z) or trans (E) form of the compound when the dashed line is a C-C double bond; and X' represents CH_2 when the dashed line is a C-C single bond, CH when the dashed line is a C-C double bond, and C when the dashed line is a C-C triple bond. X includes N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'', C-CF_3, C-OH, C-CN, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR', C-C(=O)NR'R'', C-NR'C(=O)R', C-C(=O)OR', C-OC(=O)R', C-OC(=O)NR'R'' and C-NR'C(=O)OR' where R' and R'' are individually hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, preferably methyl or ethyl). When X represents a carbon atom bonded to a substituent species, that substituent species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In certain circumstances when X represents a carbon atom bonded to a substituent species, the dashed line is a C-C double bond and the compound has the trans (E) form, the substituent species is characterized as having a sigma m value not equal to 0. Particularly when the dashed line is a C-C double bond, the compound has the trans (E) form, A, A', A'' and Z' all are hydrogen, n is 2, and Z'' is methyl, the substituent species is characterized as having a sigma m value not equal to 0. In addition, it is highly preferred that A is hydrogen, it is preferred that A' is hydrogen, and

normally A'' is hydrogen. Generally, both A and A' are hydrogen; sometimes A and A' are hydrogen, and A'' is methyl or ethyl; and often A, A' and A'' are all hydrogen. One representative compound is N-methyl-4-(3-pyridinyl)-butane-1-amine for which for which the dashed line is a C-C single bond, X' is CH_2 , X is C-H, n is 2, and A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is N-methyl-4-(3-pyridinyl)-3-butyne-1-amine for which the dashed line is a C-C triple bond, X' is C, X is C-H, n is 2, and A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Other representative compounds are (Z)-metanicotine and (E)-metanicotine, for which the dashed line is a C-C double bond, X' is CH, n is 2, and A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Of particular interest are compounds having the formula:



where n, X, A, A', A'', Z' and Z'' are as defined hereinbefore, and those compounds can have the cis (Z) or trans (E) form. For such compounds of interest, X most preferably is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0. One representative compound is (E)-4-(5-pyrimidinyl)-3-butene-1-amine for which X is N, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine for which X

is N, n is 2, A, A', A'', and Z' are each hydrogen, and Z'' is methyl. Another representative compound is (E)-N-methyl-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, and A, A', A'', and Z' are each hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-ethoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_2CH_3, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-butene-1-amine for which X is C-OCH_2CH_3, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-aminopyridin)yl]-3-butene-1-amine for which X is C-NH_2, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine for which X is C-NH_2, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-bromopyridin)yl]-3-butene-1-amine for which X is C-Br, n is 2, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine for which X is C-Br, n is 2, A, A', A'' and Z' each are hydrogen, and Z'' is methyl. Another representative compound is (E)-4-[3-(5-methoxy-6-methylpyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, A'' is methyl, and A, A', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(5-methoxy-6-methylpyridin)yl]-3-butene-1-amine for which X is C-OCH_3, n is 2, A'' and Z'' each are methyl, and A, A' and Z' each are hydrogen. Another representative compound is (E)-N-methyl-4-[3-(6-methylpyridin)yl]-3-butene-1-amin for which X is C-H, n is 2, A'' and Z'' each are methyl, and A, A' and Z' each are hydrogen. Another representative compound is (E)-4-[3-(6-methylpyridin)yl]-3-butene-1-amine for which X is C-H,

n is 2, A'' is methyl, and A, A', Z' and Z'' each are hydrogen. Another representative compound is (E)-N-methyl-5-[3-pyridinyl]-4-pentene-1-amine for which X is C-H, n is 3, Z'' is methyl, and A, A', A'' and Z' are each hydrogen. Another representative compound is (E)-N-(2-propyl)-4-[3-pyridinyl]-3-butene-1-amine for which X is C-H, n is 2, Z'' is isopropyl, and A, A', A'' and Z' are each hydrogen.

The manner in which aryl substituted aliphatic amine compounds of the present invention are synthetically produced can vary. Preparation of various aryl substituted aliphatic amine compounds can be carried out using the types of techniques disclosed by Rondahl, <u>Acta Pharm. Suec.</u>, Vol. 13, pp. 229-234 (1976). Certain metanicotine-type compounds that possess a saturated side chain rather than an olefinic side chain can be prepared by hydrogenation of the corresponding metanicotine-type compounds or the corresponding acetylenic precursors. For example, dihydrometanicotine can be prepared by hydrogenation of (E)-metanicotine as described by Kamimura et al., <u>Agr. Biol. Chem.</u>, Vol. 27, No. 10, pp. 684-688 (1963).

The manner in which aryl substituted acetylenic amine compounds of the present invention are synthetically produced can vary. For example, an aryl substituted acetylenic amine compound, such N-methyl-4-(3-pyridinyl)-3-butyne-1-amine, can be prepared using a number of synthetic steps: (i) conversion of 3-pyridinecarboxaldehyde to a 1,1-dihalo-2-(3-pyridinyl)-ethylene using a carbon tetrahalide and triphenylphosphine, (ii) side chain elaboration of this intermediate by reaction with butyl lithium and ethylene oxide, affording 4-(3-pyridinyl)-3-butyne-1-ol, (iii) conversion of this intermediate to its m thanesulfonat ester, and (iv) mesylat displacement with methyl amin , affording N-methyl-4-(3-pyridinyl)-3-butyne-1-amine.

The manner in which aryl substituted olefinic amine compounds of the present invention are synthetically produced can vary. (E)-metanicotine can be prepared using the techniques set forth by Löffler et al., Chem. Ber., Vol. 42, pp. 3431-3438 (1909) and Laforge, J.A.C.S., Vol. 50, p. 2477 (1928). Certain novel 6-substituted metanicotine-type compounds can be prepared from the corresponding 6-substituted nicotine-type compounds using the general methods of Acheson et al., J. Chem. Soc., Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The requisite precursors for such compounds, 6-substituted nicotine-type compounds, can be synthesized from 6-substituted nicotinic acid esters using the general methods disclosed by Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977). Preparation of certain 5-substituted metanicotine-type compounds can be accomplished from the corresponding 5-substituted nicotine-type compounds using the general method taught by Acheson et al., J. Chem. Soc., Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The 5-halo nicotine-type compounds (e.g., fluoro and bromo nicotine-type compounds) and the 5-amino nicotine-type compounds can be prepared using the general procedures disclosed by Rondahl, Act. Pharm. Suec., Vol. 14, pp. 113-118 (1977). The 5-trifluoromethyl nicotine-type compounds can be prepared using the techniques and materials set forth in Ashimori et al., Chem. Pharm. Bull., Vol. 38(9), pp. 2446-2458 (1990) and Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977). Furthermore, preparation of certain metanicotine-type compounds can be accomplished using a palladium catalyzed coupling reaction of an aromatic halide and a terminal olefin containing a protected amine substituent, removal of the protective group to obtain a primary amine, and optional alkylation to provide a s condary or tertiary amine. In particular, certain metanicotine-type compounds can be prepared by

subjecting a 3-halo substituted, 5-substituted pyridine compound or a 5-halo substituted pyrimidine compound to a palladium catalyzed coupling reaction using an olefin possessing a protected amine functionality (e.g., such an olefin provided by the reaction of a phthalimide salt with 3-halo-1-propene, 4-halo-1-butene, 5-halo-1-pentene or 6-halo-1-hexene). See, Frank et al., J. Org. Chem., Vol. 43(15), pp. 2947-2949 (1978) and Malek et al., J. Org. Chem., Vol. 47, pp. 5395-5397 (1982). Alternatively, certain metanicotine-type compounds can be prepared by coupling an N-protected, modified amino acid residue, such as 4-(N-methyl-N-*tert*-butyloxycarbonyl)aminobutyric acid methyl ester, with an aryl lithium compound, as can be derived from a suitable aryl halide and butyl lithium. The resulting N-protected aryl ketone is then chemically reduced to the corresponding alcohol, converted to the alkyl halide, and subsequently dehydrohalogenated to introduce the olefin functionality. Removal of the N-protecting group affords the desired metanicotine-type compound. There are a number of different methods for providing (Z)-metanicotine-type compounds. In one method, (Z)-metanicotine-type compounds can be synthesized from nicotine-type compounds as a mixture of E and Z isomers; and the (Z)-metanicotine-type compounds can then be separated by chromatography using the types of techniques disclosed by Sprouse et al., Abstracts of Papers, p. 32, Coresta/TCRC Joint Conference (1972). In another method, (Z)-metanicotine can be prepared by the controlled hydrogenation of the corresponding acetylenic compound (e.g., N-methyl-4-(3-pyridinyl)-3-butyne-1-amine). For example, certain 5-substituted (Z)-metanicotine-type compounds and certain 6-substituted (Z)-metanicotine-type compounds can be prepared from 5-substituted-3-pyridinecarboxaldehydes and 6-substitut d-3-pyridinecarboxaldehydes, respectively.

A representative compound, (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine, can be synthesized using the following representative procedure. 5-Bromonicotine (0.018 mole) in 10 ml of methylene chloride dried over phosphorous pentaoxide has a solution of ethyl chloroformate (0.018 mole) in 10 Ml of similarly dried methylene chloride added dropwise over 10 to 15 minutes. The resulting mixture then is refluxed under nitrogen atmosphere for about 3 hours. Then, the methylene chloride is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield a N-ethylcarbamate derivative of 5-bromometanicotine product as a thick liquid which has a boiling point of 182°C at 0.04 mm Hg. This product (0.08 mole) is then refluxed for several hours in 15 ml of concentrated aqueous hydrochloric acid. The resulting reaction mixture was cooled and basified to pH 8-9 using concentrated aqueous sodium hydroxide while the mixture is maintained at a temperature of about 0°C. The resulting product is extracted four times with 20 ml quantities of chloroform, and the combined collected fractions are dried over anhydrous sodium sulfate. Then, the chloroform is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield the (E)-N-methyl-4-[3-(5-bromopyridin)yl]-3-butene-1-amine product as a colorless liquid which has a boiling point of 115°C at 0.04 mm Hg. That product can be converted to a fumarate salt, which has a melting point of 148-150°C.

A representative compound, (E)-N-methyl-5-[3-pyridinyl]-4-pentene-1-amine, can be synthesized using the following representative procedure. A solution of N-methyl anabasine (0.011 mole) in 100 mL methylene chloride is added dropwise into a slight molar exc ss of ethyl chloroformate in 100 mL methylene chloride under nitrogen atmosphere in a flask equipped with a

condenser. Then, the mixture is refluxed for about 3 hours. Then, the methylene chloride is removed using a rotary evaporator, and the remaining material is distilled using a short-path distillation apparatus to yield N-ethylcarbamate of trans-homometanicotine product as a colorless liquid which has a boiling point of 170-172°C at 1 mm Hg. This product (0.012 mole) is dissolved in 50 mL concentrated aqueous hydrochloric acid, and the resulting mixture is refluxed overnight. The reaction mixture then is cooled. The resulting product is extracted four times with 20 mL quantities of chloroform, and the combined collected fractions are dried over anhydrous sodium sulfate. Then, the chloroform is removed using a rotary evaporator, and the remaining material is distilled under reduced pressure to yield the (E)-N-methyl-5-[3-pyridinyl]-4-pentene-1-amine product as a colorless liquid which has a boiling point of 81-82°C at 4 mm Hg. That product can be converted to a fumarate salt, which has a melting point of 139-140°C.

A representative compound, (E)-N-(2-propyl)-4-[3-pyridynyl]-3-butene-1-amine, can be synthesized using the following representative procedure. (E)-4-[3-pyridynyl]-3-butene-1-amine (0.5 millimole) is prepared according to the procedure of Heck, J. Org. Chem., Vol. 43, pp. 2947 (1978), combined with 2-iodopropane (0.525 millimole) and potassium carbonate (1 millimole), and refluxed in 30 mL tetrahydrofuran for 36 hours. Then, the tetrahydrofuran is removed using a rotary evaporator and 5 mL ethyl ether is added to the remaining residue. Filtration followed by concentration on a rotary evaporator yields a brown oil which can be purified by column chromatography followed by distillation und r reduced pressure (138-140°C at 0.25 mm Hg) to yield the (E)-N-(2-propyl)-4-[3-pyridynyl]-3-butene-1-amine product.

A representative compound, (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine, can be synthesized using the following representative procedure. 5- Amino nicotine (1 millimole) is prepared according to the procedure of Rondahl, Acta. Pharm. Suec., Vol. 14, pp. 113 (1977), combined with phthalic anhydride (1 millimole), and refluxed in 3 mL toluene for 16 hours using a Dean-Stark trap. The reaction mixture is cooled to ambient temperature and the toluene is removed using a rotary evaporator. To the remaining residue is added 2 mL methylene chloride, followed by dropwise addition of ethyl chloroformate (1.1 millimole) under nitrogen atmosphere. The resulting mixture is refluxed for 8 hours, cooled to ambient temperature, and concentrated on a rotary evaporator. The resulting viscous oil is heated to 160°C under vacuum for one hour, and then cooled to ambient temperature. Then, 10 mL of a 10 percent aqueous solution of sodium bicarbonate is added to the reaction mixture. That mixture then is extracted three times with 15 mL portions of chloroform. The combined portions then are dried over anhydrous potassium carbonate. Filtration followed by evaporation of chloroform yields a pale brown oil. This oil is dissolved in 1 mL tetrahydrofuran followed by 2 mL of a solution 2 parts methyl amine in 3 parts water. This mixture is stirred for 10 hours. Then, tetrahydrofuran and excess methyl amine are removed using a rotary evaporator. Concentrated aqueous hydrochloric acid (5 mL) is added to the reaction mixture followed by reflux for several hours. The acidic solution, after cooling to ambient temperature, is extracted three times with 10 mL portions of ethyl acetate. Then, the acidic solution is basified using potassium carbonate and then sodium hydroxid . The basic solution then is extracted four times with 10 mL portions of *n*-butyl alcohol. The combined extracts are dried over anhydrous magnesium

sulfate. Filtration, followed by concentration on a rotary evaporator yields the (E)-N-methyl-4-[3-(5-aminopyridin)yl]-3-butene-1-amine product as a dark brown oil. The product can be purified by column chromatography using a chloroform:methanol:triethylamine (60:20:20) solvent system as an eluent.

The present invention relates to a method for providing prevention of a CNS disorder to a subject susceptible to such a disorder, and for providing treatment to a subject suffering from a CNS disorder. In particular, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of the CNS disorder (i.e., provide protective effects), amelioration of the symptoms of the CNS disorder, and amelioration of the reoccurrence of the CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. The compounds normally are not optically active. However, certain compounds can possess substituent groups of a character so that those compounds possess optical activity. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts, such as chloride, perchlorate, ascorbate, sulfate, tartrate, fumarate, citrate, malate, lactate or aspartate salts). CNS disorders which can be treated in accordance with the present invention include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's diseas , Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder,

anxiety, dyslexia, schizophrenia and Tourette's syndrome.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics, steroids and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular CNS disorder.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al.); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); or transdermally (e.g., using a transdermal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical

composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Ciba-Geigy Corporation and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, such as a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that effect the functioning of the CNS.

The dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder. Thus, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to elicit neuropharmacological effects (e.g., elicit neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms

associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than -0.5, often are greater than about 0, and frequently are greater than about 0.5. The log P values of such typical compounds generally are less than about 3.0, often are less than about 2.5, and frequently are less than about 2.0. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and in most circumstances, cause activation of,

nicotinic cholinergic receptors of the brain of the patient. As such, such compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally exceed about 1 nM, often exceed about 200 nM, and frequently exceed about 500 nM. The receptor binding constants of such typical compounds generally are less than about 10 uM, often are less than about 7 uM, and frequently are less than about 2 uM. Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively eliciting neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, such compounds have the ability to cause relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds useful in carrying out the present invention provide for the secretion of dopamine in amounts of at least about 25 percent, often at least about 50 percent, and frequently at least about 75 percent, of that elicited by an equal molar amount of S(-) nicotine. Certain compounds of the present invention can provide secretion of dopamine in an amount which can exceed that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the

compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from muscle preparations. Thus, such compounds exhibit receptor activation constants or EC50 values (i.e., which provide a measure of the concentration of compound needed to activate half of the relevant receptor sites of the skeletal muscle of a patient) which are relatively high. Generally, typical compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue. As such, such compounds have poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, typical compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the reoccurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as demonstrated by increased effects relating to the cardiovascular system, and effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/5, and often less than 1/10, that amount sufficient to cause any side effects to a significant degree.

The following example is provided in order to further illustrate various embodiments of the invention but should not be construed as limiting the scope thereof. Unless otherwise noted, all parts and percentages are by weight.

EXAMPLE

Sample No. 1 is (E)-4-(5-pyrimidinyl)-3-butene-1-amine monofumarate (compound III monofumarat), which was prepared essentially in accordance with the following techniques.

N-3-Butene-1-phthalimide (I):

This compound was prepared essentially in accordance with the techniques described in Heck, et al., J. Org. Chem., Vol. 43, pp. 2947-2949 (1978).

(E)-N-[4-(5-Pyrimidinyl)-3-butene-1-]phthalimide (II):

Under a nitrogen atmosphere, a mixture of I (28.20 g, 140 mmol), 5-bromopyrimidine (21.63 g, 136 mmol), palladium(II) acetate (306 mg, 1.4 mmol), tri-o-tolylphosphine (828 mg, 2.7 mmol), and triethylamine (27.54 g, 272 mmol) was stirred and heated at ~ 110°C for 27 h. The precipitated brown solids were slurried in water, filtered, and dissolved in hot N,N-dimethylformamide (DMF) (75 mL). Charcoal (Darco® G-60, 1 g) was added and the mixture filtered through Celite® (1.8 g), washing the filter cake with hot DMF (10 mL). The filtrate was diluted with an equal volume of water and cooled at 5°C for 15 h. The solids were filtered, washed with water (2 x 25 mL) and dried, producing a beige, crystalline powder (28.55 g, 75.1%). Further purification, involving two recrystallizations from DMF-water (1:1), followed by two recrystallizations from toluene afforded compound II as a light beige, crystalline powder (18.94 g, 49.8%), mp 177-178.5°C.

IR (KBr): 3445 (w), 3014 (w), 2951 (w), 1768 (m, C=O), 1703 (s, C=O), 1650 (w, C=C), 1558 (m), 1433 (s), 1402 (s), 1367 (s), 1330 (m), 1057 (m), 964 (m, trans C=C), 879 (m), 721 (s, 1,2-disubst. benzene), 717 (w, 5-pyrimidinyl), 633 (w, 5-pyrimidinyl) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.60 (s, 2H), 7.85 (m, 2H), 7.70 (m, 2H), 6.35 (m, 2H), 3.85 (m, 2H), 2.63 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 168.26, 157.21, 154.09, 134.07, 131.97, 131.37, 130.69, 125.60, 123.33, 37.11, 32.49.

EI-MS: m/z (relative intensity) 279 ($M^{+\cdot}$, 5%), 160 (100%), 131 (43%), 119 (45%), 104 (17%), 77 (31%), 65 (13%), 51 (11%).

HRMS: Calcd. for $C_{16}H_{13}N_3O_2$ ($M^{+\cdot}$): m/z 279.0992. Found: 279.1008.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.68; H, 4.82; N, 14.94.

<u>(E)-4-(5-Pyrimidinyl)-3-butene-1-amine (III)</u>:

Hydrazine hydrate (2.69 g, 53.7 mmol, 99%) was added to a mixture of II (6.00 g, 21.5 mmol) and methanol (100 mL), and the mixture was stirred at ambient temperature for 27 h. The white suspension was diluted with 1M NaOH solution (400 mL) and extracted with chloroform (5 x 100 mL). The chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was vacuum dried 5 h at 55°C to give (E)-4-(5-pyrimidinyl)-3-butene-1-amine (III) as a light yellow oil (2.95 g, 92.2%), which was used without further purification.

IR (film): 3345 (br, N-H), 1655 (m, C=C), 1560 (s), 1490 (s), 1440 (s), 1415 (s), 1390 (m), 1317 (s), 1190 (m), 968 (m, trans C=C), 721 (s, 5-pyrimidinyl), 636 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 8.68 (s, 2H), 6.38 (m, 2H), 2.84 (t, 2H, J = 7 Hz), 2.40 (m, 2H), 1.26 (br s, 2H).

^{13}C NMR ($CDCl_3$): δ 157.04, 153.96, 133.16, 130.92, 124.82, 41.36, 37.44.

EI-MS: m/z (relative intensity) 148 ($M^{+\cdot}$-1, 0.1%), 132 (1%), 120 (100%), 93 (31%), 66 (40%), 51 (11%), 44 (14%).

The monofumarate of III was prepared by adding a warm solution of fumaric acid (156 mg, 1.34 mmol) in ethanol (5 mL) to a warm solution of III (100 mg, 0.67 mmol) in ethanol (3 mL). The mixture was concentrated by rotary evaporation, and the slightly

yellow solids were recrystallized from ethanol-ether (1:1). The solids were filtered, washed with ethanol, ether, and vacuum dried at 50°C for 24 h, affording the monofumarate as a white, crystalline powder (63.8 mg, 35.9%), mp 160-161.5°C.

IR (KBr): 3300-2300 (br, s, amine-carboxylate), 1705 (s, C=O), 1664 (s), 1606 (s, C=C), 1556 (s), 1409 (s, fumarate), 1254 (m), 1186 (m), 981 (m, trans C=C), 852 (m), 796 (m), 723 (w, 5-pyrimidinyl), 648 (m, fumarate), 631 (m, 5-pyrimidinyl) cm^{-1}.

^{1}H NMR (D_2O): δ 9.00 (s, 1H), 8.84 (s, 2H), 6.69 (s, 2H), 6.63 (d, 1H, J = 16.4 Hz), 6.52 and 6.46, (dt, 1H, J = 16.1, 6.8 Hz), 3.20 (m, 2H), 2.72 (m, 2H).

^{13}C NMR (D_2O): δ 171.45, 154.10, 134.63, 131.04, 130.23, 126.05, 38.40, 30.33.

Anal. Calcd. for $C_8H_{11}N_3 \cdot C_4H_4O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.24; H, 5.75; N, 15.65.

Sample No. 2 is (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine (compound VI), which was prepared essentially in accordance with the following techniques.

<u>(E)-N-tert-Butyloxycarbonyl-4-(5-pyrimidinyl)-3-butene-1-amine (IV)</u>:

A solution of di-<u>tert</u>-butyl dicarbonate (2.66 g, 12.2 mmol) in methylene chloride (10 mL) was added dropwise over 5 min to a stirring solution of (E)-4-(5-pyrimidinyl)-3-butene-1-amine (III) (1.70 g, 11.4 mmol) in methylene chloride at 0°C. The yellow solution was stirred at 0°C for 15 min and at ambient temperature for 22 h. Concentration by rotary evaporation, followed by vacuum drying at 30°C for 15 h afforded a y llow oil. The oil was chromatographed on silica gel (165 g), luting first with ethyl acetate to remove impurities. Elution with chloroform-methanol (2:1) afforded the product which was re-chromatographed

eluting with ethyl acetate. Selected fractions were combined in chloroform and concentrated by rotary evaporation. The residue was vacuum dried at 35°C for 48 h to give compound IV as a light yellow oil (2.56 g, 90.1%), which crystallized upon cooling, affording a light yellow, crystalline solid, mp 54-55.5°C.

IR (KBr): 3030 (w), 2990 (w), 2980 (w), 2965 (w), 2935 (w), 3298 (s, amide N-H), 1712 (s, carbamate C=O), 1657 (w, C=C), 1560 (s), 1535 (s, amide N-H), 1433 (s), 1414 (s), 1367 (s, tert-butyl), 1275 (s, amide N-H), 1246 (s, ester C-O), 1174 (s, ester C-O), 1149 (s), 1111 (m), 987 (m), 966 (m trans C=C), 723 (w, 5-pyrimidinyl), 636 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.05 (s, 1H), 8.70 (s, 2H), 6.37 (m, 2H), 4.59 (br s, 1H), 3.30 (m, 2H), 2.43 (m, 2H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 157.34, 156.83, 155.84, 154.18, 153.79, 132.24, 130.75, 125.15, 79.42, 39.64, 34.05, 28.56, 28.20.

EI-MS: m/z (relative intensity) 249 ($M^{+\cdot}$, 0.1%), 193 (15%), 176 (24%), 132 (16%), 120 (79%), 119 (85%), 93 (19%), 65 (24%), 57 (100%).

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.61; H, 7.62; N, 16.78.

<u>(E)-N-Methyl-N-tert-Butyloxycarbonyl-4-(5-pyrimidinyl)-3-butene-1-amine (V):</u>

Under a nitrogen atmosphere, sodium hydride (0.78 g, 19.5 mmol, 60% dispersion in oil) was added to a stirring solution of IV (0.50 g, 2.0 mmol), 1,2-dimethoxyethane (20 mL), DMF (25 mL), and a trace of diisopropylamine. The mixture was stirred at ambient temperature for 45 min, and a solution of iodomethane (2.59 g, 18.3 mmol) in 1,2-dimethoxyethane (5 mL) was added. The mixtur was stirred at ambient temperature for 3 days, cooled, and water (25 mL) was added dropwise. The mixture was diluted with water (200 mL)

and extracted with chloroform (7 x 50 mL). All chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The residue was dried under high vacuum at ambient temperature to give a red-brown oil. The oil was chromatographed on silica gel (50 g), eluting with ethyl acetate. Selected fractions were combined, concentrated by rotary evaporation, and dried under high vacuum at ambient temperature to give compound V as a light yellow oil (0.40 g, 76.1%).

IR (film): 3650-3200 (br, w), 2980 (m), 2940 (m), 1697 (s, carbamate C=O), 1556 (s), 1484 (s), 1452 (s), 1420 (s, N-CH_3), 1411 (s, tert-butyl), 1394 (s, tert-butyl), 1369 (s), 1304 (m), 1249 (m, ester C-O), 1218 (m), 1163 (s, ester C-O), 1136 (s), 972 (m, trans C=C), 883 (m), 774 (m), 721 (m, 5-pyrimidinyl), 631 (m, 5-pyrimidinyl) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.63 (s, 2H), 6.31 (m, 2H), 3.32 (m, 2H), 2.82 (s, 3H), 2.44 (m, 2H), 1.39 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 157.06, 155.70, 153.95, 132.49, 130.94, 124.73, 79.51, 34.38, 28.45.

EI-MS: m/z (relative intensity) 263 ($M^{+\bullet}$, 0.3%), 207 (5%), 190 (7%), 144 (24%), 133 (9%), 120 (39%), 93 (13%), 88 (15%), 65 (11%), 57 (100%), 44 (89%).

HRMS: Calcd. for $C_{14}H_{21}N_3O_2$ ($M^{+\bullet}$): m/z 263.1634. Found: 263.1643.

(E)-N-Methyl-4-(5-pyrimidinyl)-3-butene-1-amine (VI):

Under a nitrogen atmosphere, iodotrimethylsilane (0.50 g, 2.5 mmol) was added dropwise, at ambient temperature, to a stirring solution of V (0.33 g, 1.2 mmol) in chloroform (20 mL). The r d-brown mixture was stirred 30 min and methanol (20 mL) was add d. The mixture was stirred 1 h and concentrated by rotary evaporation. The residue was

basified with 1M NaOH solution (25 mL) and extracted with chloroform (7 x 25 mL). The chloroform extracts were combined, dried (Na_2SO_4) and concentrated by rotary evaporation, affording a brown oil. The oil was chromatographed on silica gel (35 g), eluting with methanol-ammonium hydroxide (10:1). Selected fractions were combined, vacuum dried at 45°C for 3 h, affording (E)-N-methyl-N-4-(5-pyrimidinyl)-3-butene-1-amine (VI) as a brownish-yellow oil (0.12 g, 59.6%).

IR (film): 3148 (br, s, N-H), 1653 (s, C=C), 1560 (s), 1473 (m), 1435 (s), 1414 (s, N-CH_3), 970 (m, trans C=C), 721 (s, 5-pyrimidinyl), 636 (s, 5-pyrimidinyl) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.02 (s, 1H), 8.68 (s, 2H), 6.37 (m, 2H), 2.76 (t, 2H, J = 6.8 Hz), 2.46 (m, 5H, including a N-CH_3 singlet), 1.65 (br s, 1H).

^{13}C NMR ($CDCl_3$): δ 157.09, 154.01, 132.99, 130.90, 124.81, 50.76, 36.06, 33.35.

EI-MS: m/z (relative intensity) 146 (0.3%), 132 (0.4%), 120 (22%), 93 (4%), 65 (4%), 44 (100%).

HRMS: Calcd. for $C_7H_8N_2$ ($M^{+\cdot}$ - 44): m/z 120.0676. Found: 120.0687.

Sample No. 3 is (E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine monofumarate (compound IX monofumarate), which was prepared essentially in accordance with the following techniques:

<u>3-Bromo-5-methoxypyridine (VII)</u>:

This compound was prepared essentially in accordance with the techniques described in Comins et al., *J. Org. Chem.*, Vol. 55, pp. 69-73 (1990).

<u>(E)-N-4-[3-(5-methoxypyridin)yl]-3-butene-1-phthalimide (VIII)</u>:

Und r a nitrogen atmosph re, a mixture of N-3-butene-1-phthalimide (I) (5.51 g, 27.4 mmol), 3-

bromo-5-methoxypyridine (VII) (5.00 g, 26.6 mmol), palladium(II) acetate (59.7 mg, 0.27 mmol), tri-o-tolylphosphine (162 mg, 0.53 mmol), and triethylamine (5.38 g, 53.2 mmol) was stirred and heated at ~ 100°C for 21 h. The precipitated brown solids were slurried in water, filtered, and dissolved in hot DMF (30 mL). The mixture was filtered through Celite® (1 g), washing the filter cake with hot DMF (10 mL). The filtrate was diluted with an equal volume of water and cooled at 5°C for 15 h. The solids were filtered, washed with water (2 x 10 mL), cold ethanol (10 mL), and dried, producing a beige, crystalline powder (7.79 g, 95.0%). Further purification, involving two recrystallizations from DMF-water (1:1) afforded compound VIII as a light beige, crystalline powder (5.36 g, 65.4%), mp 148-151°C. An analytical sample was recrystallized from toluene, affording a light beige, crystalline powder, mp 148-151.5°C.

IR (KBr): 3440 (w), 3040 (m), 2960 (s), 2940 (s), 2825 (w), 1766 (m, C=O), 1700 (s, C=O), 1654 (m, C=C), 1580 (m, pyridinyl), 1455 (s), 1420 (s), 1320 (m), 1190 (m), 1000 (s), 973 (s, trans C=C), 867 (s, 3,5-disubst. pyridine), 723 (s, 1,2-disubst. benzene), 703 (s, 3,5-disubst. pyridine) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8.14 (s, 1H), 8.08 (s, 1H), 7.82 (m, 2H), 7.69 (m, 2H), 7.10 (dd, 1H, J = 2.4, 2.0 Hz), 6.38 (d, 1H, J = 16.1 Hz), 6.25 and 6.20 (dt, 1H, J = 15.9, 6.8 Hz), 3.84 (t, 5H, including an O-CH_3 singlet, J = 7.1 Hz), 2.62 (dq, 2H, J = 7.1, 1.0 Hz).

^{13}C NMR ($CDCl_3$): δ 168.27, 155.73, 140.72, 136.45, 133.96, 132.05, 129.00, 123.26, 116.80, 55.52, 37.34, 32.30.

EI-MS: m/z (relative intensity) 308 (M^{+}, 13%), 160 (100%), 148 (8%), 133 (10%), 105(8%), 77 35 (15%).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.34; H, 5.29; N, 9.00.

(E)-4-[3-(5-methoxypyridin)yl]-3-butene-1-amine (IX):

Hydrazine hydrate (245 mg, 4.90 mmol, 99%) was added to a mixture of VIII (500 mg, 1.62 mmol) and methanol (20 mL), and the mixture was stirred at ambient temperature for 20 h. The gray suspension was diluted with 1M NaOH solution (190 mL) and extracted with chloroform (5 x 25 mL). The chloroform extracts were combined, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude product (287 mg) was further purified by vacuum distillation, affording compound IX (183 mg, 62.3%) as a light yellow oil, bp 110°C at 0.05 mm Hg.

IR (film): 3350 (br, s), 3035 (s), 2940 (s), 2840 (m), 1585 (s), 1460 (s), 1425 (s), 1320 (s), 1295 (s, ArO-CH_3), 1185 (m), 1160 (m), 1050 (m), 1020 (sh), 965 (s, trans C=C), 885 (m, 3,5-disubst. pyridine), 820 (w), 710 (m, 3,5-disubst. pyridine).

^{1}H NMR ($CDCl_3$): δ 8.16 (d, 1H, J = 2.0 Hz), 8.13 (d, 1H, J = 2.9 Hz), 7.14 (dd, 1H, J = 2.6, 2.0 Hz), 6.41 (d, 1H, J = 15.9 Hz), 6.27 and 6.22 (dt, 1H, J = 15.9, 7.1 Hz), 3.84 (s, 3H), 2.84 (t, 2H, J = 6.6 Hz), 2.36 (dq, 2H, J = 6.6, 1.0 Hz).

^{13}C NMR ($CDCl_3$): 155.79, 140.70, 136.24, 133.72, 130.79, 128.27, 116.91, 55.57, 37.29, 29.70.

EI-MS: m/z (relative intensity) 178 ($M^{+\cdot}$, 0.4%), 149 (88%), 148 (100%), 133 (12%), 105 (9%), 78 (10%).

The monofumarate of IX was prepared by adding a warm solution of fumaric acid (131 mg, 1.12 mmol) in 2-propanol (15 mL) to compound IX (166 mg, 0.93 mmol). After stirring 30 min, the solution was concentrated by rotary evaporation to a white powder. The crude product was recrystallized from 2-propanol, and the mixture was stor d at ambient temperature for 15 h. The solids were filter d, washed with cold 2-propanol, ether, and vacuum dried at 50°C for 6 h, affording the

monofumarate as a white, crystalline powder (177 mg, 64.6%), mp 151-153°C.

IR (KBr): 3300-2400 (br, s, amine-carboxylate), 1700 (s, C=O), 1630 (s, C=O), 1570 (sh), 1535 (m), 1460 (m), 1435 (m), 1290 (s, ArO-CH_3), 1158 (m), 1040 (m), 982 (s, trans C=C), 875 (m, 3,5-disubst. pyridine), 793 (m), 705 (m, 3,5-disubst. pyridine), 652 (m).

^{1}H NMR (D_2O): δ 8.31 (s, 1H), 8.25 (s, 1H), 7.85 (s, 1H), 6.68 (d, 1H, J = 16.1 Hz), 6.57 (s, 2H), 6.53 and 6.48 (dt, 1H, J = 15.9, 7.1 Hz), 3.98 (s, 3H), 3.21 (t, 2H, J = 7.1 Hz), 2.68 (q, 2H, J = 7.1 Hz).

^{13}C NMR (D_2O): δ 172.93, 156.77, 136.17, 135.62, 134.90, 131.81, 130.25, 128.04, 122.44, 56.31, 38.54, 30.14.

Anal. Calcd. for $C_{10}H_{14}N_2O \cdot C_4H_4O_4$: C, 57.14; H, 6.16; N, 9.52. Found: C, 56.91; H, 6.18; N, 9.51.

Sample No. 4 is N-Methyl-4-(3-pyridinyl)-3-butyne-1-amine which was prepared essentially in accordance with the following techniques.

<u>1,1-Dibromo-2-(3-pyridinyl)-ethylene (X)</u>:

Tetrabromomethane (24.82 g, 0.747 mole) and triphenylphosphine (39.17 g, 0.149 mole) were stirred together in dry methylene chloride (100 mL) for 5 min. at 0°C under a nitrogen atmosphere. To this mixture was added dropwise pyridine 3-carboxaldehyde (4 g, 0.0373 mole). The solution was then stirred for 45 min. at ambient temperature. The reaction mixture was extracted with aqueous 6N hydrochloric acid (3 x 25 mL), the aqueous layer basified with solid sodium bicarbonate to pH 8-9 and extracted with chloroform (4 x 25 mL). The combined organic liquors were dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator to give a dark colored syrup. The crude product was chromatographed on silica gel (70-230 mesh) with chloroform:methanol (95:5) as eluant, to

afford a light yellow solid (5.0 g, 70%) which rapidly turned dark on standing.

^1H NMR($CDCl_3$) δ 8.65 (s, H), 8.58 (d, 1H), 8.00 (d, 1H), 7.45 (s, 1H), 7.22-7.36 (m, 1H).

Anal. calcd. for $C_7H_4NBr_2$: C, 31.94; H, 1.90; N, 5.32; Br, 60.84. Found: C, 32.11; H, 2.03; N, 5.50; Br, 60.99.

<u>4-(3-Pyridinyl)-3-butyne-1-ol (XI)</u>:

To dry THF (10 mL) contained in a 50 mL round-bottomed flask fixed with a nitrogen gas balloon was added X (2.5 g, 0.01 mole). The flask was cooled to -78°C in an acetone-dry ice bath, and n-butyl lithium in THF (22 mL of a 2.5 molar solution in THF) was added dropwise via a syringe during constant stirring. After addition, the solution was stirred for 1 hour. The reaction mixture temperature was then adjusted to -60°C and ethylene oxide (1 mL) was added in one portion, and the reaction was allowed to warm to ambient temperature with stirring. The resulting reaction mixture was quenched with water (10 mL) and extracted with chloroform (3 x 25 mL), the combined organic liquors dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator under reduced pressure. The resulting oil was chromatographed on silica gel to afford the product as a light brown liquid (590 mg, 40%).

^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.49 (d, 1H), 7.68 (d, 1H) 7.29-7.36 (m, 1H), 3.92 (t, 2H), 2.80(m, 5H).

Anal. calcd. for C_9H_9NO: C, 73.46; H, 6.12; N, 9.52. Found: C, 73.61; H, 6.31; N, 9.66.

<u>Methanesulfonate ester of 4-(3-Pyridinyl)-3-butyne-1-ol (XII)</u>:

In dry methylen chloride (2 mL) was dissolved XI (0.15 g, 1.0 mmole), and to this solution

was added triethylamine (0.184 ml, 1.3 mmole). The reaction was stirred overnight under nitrogen atmosphere. The mixture was cooled to 4°C and methane sulfonyl chloride (0.15 g, 1.3 mmole) was added. The reaction mixture was then poured over ice/water (10 mL) and the resulting mixture stirred for 5 min. To this mixture was added saturated aqueous sodium bicarbonate solution (5 mL) chilled to 4°C, and the mixture stirred for 30 min., then extracted with chloroform (4 x 10 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and the volume concentrated on a rotary evaporator. The product was further purified using gel chromatography, eluting with a chloroform: methanol mixture containing 1% triethylamine. Yield of XII is 0.218 g (about 97%).

^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 7.62 (d, 1H), 7.18-7.22 (m, 1H), 4.31 (t, 2H), 3.00 (s, 3H), 2.80 (t, 2H).

<u>N-Methyl-4-(3-pyridinyl)-3-butyne-1-amine (XIII)</u>:

An aqueous methylamine solution (5mL, 40%, 58.7 mmole) was mixed with XII (200 mg, 0.08 mmole) and stirred for 3 hr. in a sealed tube at 45°C. After the reaction was complete, water (10 mL) was added to the cooled reaction mixture, and the reaction mixture was extracted with chloroform (10 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was chromatographed on a silica gel column using methanol:chloroform (1:9) and then with a chloroform:methanol mixture containing 1% triethylamine as eluent. About 70 mg of XIII was obtained as a slightly yellow syrup, which was distilled at 110 - 112°C, 0.04 mm Hg. XIII was converted to its mono fumarate salt form, which exhibits a melting point of 103-104°C.

Free base. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.48 (d, 1H), 7.62 (d, 1H), 7.20 (t, 1H), 2.82 (t, 2H), 2.61 (t, 2H), 2.33 (s, 3H), 1.4 (br s, 1H).

Fumarate salt. ^{1}H NMR (D_2O) δ 8.51 (s, 1H), 8.89 (d, 1H), 7.91 (d, 1H), 7.40 (m, 1H), 6.28 (s, 2H), 3.20 (t, 2H), 2.80 (t, 2H), 2.62 (s, 3H).

^{13}C NMR (D_2O) δ 164.5, 151.8, 148.0, 146.0, 138.8, 128.2, 124.5, 93.0, 82.3, 50.4, 36.2, 20.1.

Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.70; N, 10.14. Found: C, 60.84; H, 5.72; N, 10.23.

Sample No. 5 is (Z)-metanicotine which was prepared essentially in accordance with the following techniques.

<u>(Z)-Metanicotine (XIV)</u>:

Into a hydrogenation bottle together with methanol (20 mL), glacial acetic acid (1 mL) and a catalytic amount of quinoline was placed XIII free base (200 mg, 1.25 mmole). Lindlar's catalyst (palladium/calcium carbonate poisoned with lead) (60 mg) was added and the mixture hydrogenated at 50 psig in a Parr reaction apparatus overnight at ambient temperature. The catalyst was filtered off, the resulting solution basified with aqueous sodium hydroxide (50% w/v) to a pH 8-9, and then extracted with chloroform (3 x 25 mL). The combined organic liquors were concentrated on a rotary evaporator, and the residue chromatographed on 60-230 mesh silica gel, using chloroform:methanol: triethylamine (90:10:1) as eluent, to afford XIV as a colorless oil at about 100% yield. XIV is converted to its mono fumarate salt, which has a melting point of 117-118°C.

Free base. ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.42 (d, 1H), 7.60 (d, 1H), 7.22 (m, 1H), 6.81 (m, 1H), 6.51 (d, 1H), 2.79 (t, 2H), 2.52 (m, 2H), 2.41 (s, 3H).

Difumarate salt. ^{1}H NMR (D_2O) δ 8.48 (br s, 2H), 8.10 (d, 1H), 7.75-7.63 (m, 1H), 6.52 (d, 1H),

6.40 (s, 1H), 5.85-5.78 (m, 1H), 3.00 (t, 2H), 2.51 (m, 5H).

Anal. calcd. for $C_{10}H_{14}N_2.2C_4H_4O_4$: C, 54.82; H, 5.58; N, 7.10. Found: C, 54.47; H, 5.68; N, 6.98.

Sample No. 6 is (E)-N-methyl-4-[3-(6-methylpyrindin)yl]-3-butene-1-amine which was prepared essentially in accordance with the following techniques.

6-Methylmyosmine (XV):

Sodium hydride (60% in oil) (1.9 g, 0.079 mole) was placed in a 250 mL two-necked round bottom flask and washed with dry THF (50 mL). A further aliquot of dry THF (100 mL) was added followed by a solution of N-vinylpyrrolidone (4.7 g, 0.04 mole) in dry THF (30 mL), and the mixture stirred for 30 min. at ambient temperature. A solution of ethyl 6-methylnicotinate (5.0 g, 0.033 mole) in dry THF (20 mL) was then added dropwise over 10 min., during which time evolution of hydrogen occurred. The reaction was flushed with nitrogen, and the mixture refluxed for 6 hr. After cooling, aqueous hydrochloric acid (6N, 25 mL) was added and the THF removed by rotory evaporation under reduced pressure. A further volume of aqueous hydrochloric acid (6N, 20 mL) was added and the mixture refluxed overnight. On cooling, the mixture was basified with aqueous sodium hydroxide (50% w/v) to pH 8-9, and XV was extracted with chloroform (5 x 20 mL). The combined organic liquors were dried over anhydrous sodium sulfate, filtered and the solvent evaporated to afford XV, which was crystallized from methanol as a tan solid (4.45 g, 84%).

^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.15 (d, 1H), 7.20 (d, 1H), 4.12 (t, 2H), 2.98 (t, 2H), 2.80 (s, 3H), 2.00 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 172.5, 160.08, 148.1, 135.01, 122.7, 61.5, 34.8, 24.2, 22.2.

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.00, H, 7.50; N, 17.50. Found: C, 74.94; H, 7.51; N, 17.47.

<u>(+/-)-6-Methylnornicotine (XVI)</u>:

Into a round bottom flask was placed XV (3.0 g, 0.018 mole), methanol (20 mL) and glacial acetic acid (4 mL). The mixture was cooled to -78°C in a dry ice-acetone bath, and sodium borohydride (1.332 g, 0.36 mole) was added over 30 min. After addition, the reaction mixture was allowed to warm to ambient temperature, and stirred for 1 hr. The methanol then was removed on a rotary evaporator under reduced pressure and the residue was basified with aqueous sodium hydroxide (50% w/v) to pH 8-9. The aqueous solution was extracted with chloroform (5 x 25 mL) and the combined organic liquors dried over anhydrous sodium sulfate, filtered and evaporated on a rotary evaporator to afford XVI as a dark brown liquid, which was distilled at 4 mm Hg to yield a clear, colorless liquid (b.p. is 113-114°C, 4mm Hg) (2.43 g, 80%).

^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 7.60 (d, 1H), 7.10 (d, 1H), 4.15 (t, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.30 (s, 3H), 2.20-2.00 (m, 3H), 2.00-1.98 (m, 2H), 1.78-1.60 (m, 2H).

$HClO_4$ salt ^{1}H NMR (D_2O) δ 8.62 (s, 1H), 8.40 (d, 1H), 7.81 (d, 1H), 3.58 (t, 2H), 2.78 (s, 3H), 2.40-2.20 (m, 4H).

Anal. calcd. for $C_{10}H_{16}N_2Cl_2O_8$: C, 33.05; H, 4.40; N, 7.71; Cl, 19.55. Found: C, 33.16; H, 4.46; N, 7.64; Cl, 19.43.

<u>(+/-)-6-Methylnicotine (XVII)</u>:

Into a round bottom flask was placed XVI (2.0 g), and formaldehyd (37% w/v in water, 20 mL) and formic acid (95-97 % w/v, 45 mL), both a 0°C, were added. The mixture th n was refluxed under nitrogen for 8 hr. The cooled reaction mixture was basified

with aqueous sodium hydroxide (50% w.v) to pH 8-9, and the solution extracted with chloroform (5 x 25 mL). The combined organic liquors were dried over anhydrous sodium sulfate, filtered and evaporated; and the resulting oil distilled under reduced pressure to afford XVII as a clear odorless oil (b.p. 107°C at 3 mm Hg, 92 % yield).

^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.60 (d, 1H), 7.12 (d, 1H), 3.15 (t, 1H), 3.00 (t, 1H), 2.56 (s, 3H), 2.40-2.20 (m, 1H), 2.18-2.08 (m, 4H), 2.00 - 1.92 (m, 1H), 1.80-1.60 (m, 2H).

$HClO_4$ salt. Anal. calcd. for $C_{11}H_{18}N_2Cl_2O_8$: C, 35.01; H, 4.77; N, 7.42; Cl, 18.83.
Found: C, 35.12; H, 4.85; N, 7.37; Cl, 18.76.

<u>N-Ethylcarbamate of (+/-)-6-methylmetanicotine (XVIII)</u>:

To a stirred solution of XVII (3.0 g, 0.017 mole) in methylene chloride (25 mL) under nitrogen atmosphere was added dropwise a solution of ethylchloroformate (2.40 g) in methylene chloride (10 mL) at ambient temperature. The mixture was refluxed for 4 hr. After evaporation of solvent on a rotary evaporator under reduced pressure, the resulting oil was vacuum distilled to give XVIII as a thick viscous liquid (b.p. 172-175°C, 4 mm Hg), which was further purified by silica column chromatography, to yield about 3 g of XVIII (70% yield).

^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.61 (d, 1H), 7.08 (d, 1H), 6.60 (d, 1H), 6.08-6.00 (m, 1H), 4.18 (q, 2H), 3.40 (m, 2H), 2.91 (s, 3H), 2.60-2.42 (m, 5H), 1.22 (t, 3H).

<u>(E)-N-methyl-4-[3-(6-methylpyridin)yl]-3-butene-1-amine (XIX)</u>:

Into a round bottom flask was placed XVIII (3.0 g, 0.012 mole), and concentrated hydrochloric acid (15 mL) was added. The mixture was refluxed overnight,

and the resulting solution basified with aqueous sodium hydroxide (50% w/v) to pH 8-9. The solution was extracted with chloroform (4 x 25 mL), the combined organic liquors dried over anhydrous sodium carbonate, filtered, and the solvent evaporated to afford an oil. Vacuum distillation of the oil afforded XIX as a clear, colorless liquid (b.p. 80°C at 0.2 mm Hg, 78% yield). XIX then was provided in the form of a monofumarate salt, m.p. 134-135°C.

Difumarate salt. ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 7.76 (d, 1H), 7.20 (d, 1H), 6.52-6.24 (m, 4H), 3.00 (t, 2H), 2.60-2.00 (m, 3H).

Anal. Calcd. for $C_{11}H_{16}N_2.2C_4H_4O_4$: C, 55.88; H, 5.88; N, 6.86. Found: C, 55.72; H, 5.93; N, 6.83.

Sample No. 7 is N-methyl-(3-pyridinyl)-butane-1-amine, which was prepared essentially in accordance with the following techniques.

(E)-Metanicotine (0.4 g, 2.46 mmole) was dissolved in a mixture of methanol (20 mL) and glacial acetic acid (1 mL) and 5% Pd-C catalyst (30 mg) was added. The mixture was hydrogenated at 50 psig hydrogen for 2 hr. The reaction mixture then was filtered and the solvent removed on a rotary evaporator. To the residue was added water (5 mL) and the aqueous solution basified to pH 8-9 with 40% aqueous sodium hydroxide. The mixture then was extracted with chloroform (5 x 10 mL), and the combined organic liquors dried over potassium carbonate, filtered and solvent was evaporated under reduced pressure on a rotovaporator. The resulting oil then was provided in the form of a difumarate salt, melting point being 115-116°C.

Free base. ^{1}H NMR ($CDCl_3$) δ 8.42 (m, 2H), 7.50 (d, 1H), 7.20 (m, 1H), 2.64-2.58 (m, 4H), 2.40 (s, 3H), 2.78-2.60 (m, 2H), 2.42-2.59 (m, 2H), 1.22 (broad s, 1H).

Difumarate salt. ^1H NMR (D_2O) δ 8.64 (d, 2H), 8.43 (d, 1H), 8.00 (m, 1H), 6.62 (s, 4H), 3.24 (t, 2H), 2.90 (t, 2H), 2.70 (s, 3H), 1.81-1.69 (m, 4H).

Anal. calcd. for $C_{10}H_{16}N_2 . 2C_4H_4O_4 . 1/2H_2O$: C, 53.33; H, 6.17; N, 6.91. Found: C, 53.33; H, 6.06; N, 7.07.

Sample No. 8 is (E)-metanicotine which was provided generally using the techniques set forth by Laforge, J.A.C.S., Vol. 50, p. 2477 (1928).

For comparison purposes, Sample No. C-1 was provided. This sample is (S)-(-)-nicotine, which has been reported to have demonstrated a positive effect towards the treatment of various CNS disorders.

Determination of binding of compounds to relevant receptor sites:

Rats (Sprague-Dawley) were maintained on a 12 hour light/dark cycle and were allowed free access to water and food supplied by Wayne Lab Blox, Madison, WI. Animals used in the present studies weighed 200 to 250 g. Brain membrane preparations were obtained from brain tissue of either males or females.

Rats were killed by decapitation following anesthesia with 70% CO_2. Brains were removed and placed on an ice-cold platform. The cerebellum was removed and the remaining tissue was placed in 10 volumes (weight:volume) of ice-cold buffer (Krebs-Ringers HEPES: NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 2.5 mM; $MgSO_4$, 1.2 mM; HEPES, 20 mM; pH to 7.5 with NaOH) and homogenized with a glass-Teflon tissue grinder. The resulting homogenate was centrifuged at 18,000 x g for 20 min. and the resulting pellet was resuspended in 20 volumes of water. After 60 min. incubation at 4 °C, a new pellet was collected by centrifugation at 18,000 x g for 20 min. After resuspension in 10 volumes of buffer, a new final pellet was again collected by centrifugation at 18,000 x g for 20 min. Prior to each

centrifugation step, the suspension was incubated at 37°C for 5 min. to promote hydrolysis of endogenous acetylcholine. The final pellet was overlayered with buffer and stored at -70°C. On the day of the assay, that pellet was thawed, resuspended in buffer and centrifuged at 18,000 x g for 20 min. The pellet obtained was resuspended in buffer to a final concentration of approximately 5 mg protein/ml. Protein was determined by the method of Lowry et al., J. Biol. Chem., Vol. 193, pp. 265-275 (1951), using bovine serum albumin as the standard.

The binding of L-[^{3}H]nicotine was measured using a modification of the method of Romano et al., Science, Vol. 210, pp. 647-650 (1980) as described previously by Marks et al., Mol. Pharmacol., Vol. 30, pp. 427-436 (1986). The L-[^{3}H]nicotine used in all experiments was purified chromatographically by the method of Romm, et al., Life Sci., Vol. 46, pp. 935-943 (1990). The binding of L-[^{3}H]nicotine was measured using a 2 hr. incubation at 4°C. Incubations contained about 500 ug of protein and were conducted in 12 mm x 75 mm polypropylene test tubes in a final incubation volume of 250 ul. The incubation buffer was Krebs-Ringers HEPES containing 200 mM TRIS buffer, pH 7.5. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (Micro Filtration Systems) that had been soaked in buffer containing 0.5 percent polyethyleneimine. Filtration vacuum was -50 to -100 torr. Each filter was washed five times with 3 ml of ice-cold buffer. The filtration apparatus was cooled to 2°C before use and was kept cold through the filtration process. Nonspecific binding was determined by inclusion of 10 uM nonradioactive nicotine in the incubations.

The inhibition of L-[^{3}H]nicotin binding by test compounds was det rmined by including one of eight different concentrations of the test compound in the

incubation. Inhibition profiles were measured using 10 nM L-[^{3}H]nicotine and IC_{50} values were estimated as the concentration of compound that inhibited 50 percent of specific L-[^{3}H]nicotine binding. Inhibition constants (Ki values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

Determination of Dopamine Release:

Dopamine release was measured by preparing synaptosomes from the striatal area of rat brain obtained from Sprague-Dawley rats generally according to the procedures set forth by Nagy et al., J. Neurochem., Vol. 43, pp. 1114-1123 (1984). Striata from 4 rats were homogenized in 2 ml of 0.32M sucrose buffered with 5 mM HEPES (pH 7.5), using a glass-Teflon tissue grinder. The homogenate was diluted to 5 ml with additional homogenization solution and centrifuged at 1,000 x g for 10 min. This procedure was repeated on the new pellet and the resulting supernatant was centrifuged at 12,000 x g for 20 min. A 3 layer discontinuous Percoll gradient consisting of 16 percent, 10 percent and 7.5 percent Percoll in HEPES-buffered sucrose was made with the final pellet dispersed in the top layer. After centrifugation at 15,000 x g for 20 min., the synaptosomes were recovered above the 16 percent layer with a Pasteur pipette, diluted with 8 ml of perfusion buffer (128 mM NaCl, 2.4 mM KCl, 3.2 Mm $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25 mM HEPES pH 7.4, 10 mM dextrose, 1 mM ascorbate, 0.01 mM pargyline), and centrifuged at 15,000 x g for 20 min. The new pellet was collected and re-suspended in perfusion buffer. The synaptosome suspension was incubated for 10 min. at 37°C. [^{3}H]-Dopamine (Amersham, 40-60 Ci/mmol) was added to th suspension to give a final concentration of 0.1 uM, and the suspension was incubated for another 5 min. Using this

method, 30 to 90 percent of the dopamine was taken up into the synaptosomes, as determined by scintillation counting following filtration through glass fiber filters soaked with 0.5 percent polyethyleneimine. A continuous perfusion system was used to monitor release following exposure to each ligand. Synaptosomes were loaded onto glass fiber filters (Gelman type A/E). Perfusion buffer was dripped onto the filters (0.2-0.3 ml/min.) and pulled through the filters with a peristaltic pump. Synaptosomes were washed with perfusion buffer for a minimum of 20 min. before addition of the ligand. After the addition of 0.2 ml of a solution containing various concentrations of ligand, the perfusate was collected into scintillation vials at 1 min. intervals and the dopamine released was quantified by scintillation counting. Peaks of radioactivity released above background were summed and the average basal release during that time was subtracted from the total. Release was expressed as a percentage of release obtained with an equal concentration of (S)-(-)-nicotine.

Determination of Log P:

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968)), were calculated according to the methods described by Hopfinger, Conformational Properties of Macromolecules, Academic Press (1973) using Cerius^2 software package by Molecular Simulations, Inc. for Sample Nos. 1-3, 5-8 and C-1, and Bodor, University of Florida (1991) using the BlogP software package by CAChe Scientific, Inc. for Sample No. 4.

Determination of Interaction with Muscle

Human muscle activation was established on the human clonal line TE671/RD which is derived from an embryonal rhabdomyosarcoma (Stratton et al., Carcinogen, Vol. 10, pp. 899-905 (1989)). As evidenced through pharmacological (Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989)), electrophysiological (Oswald et al, Neurosci. Lett., Vol. 96, pp. 207-212 (1989)), and molecular biological studies (Luther et al., J. Neurosci., Vol. 9, pp. 1082-1096 (1989)) these cells express muscle-like nicotinic receptors. Nicotinic acetylcholine receptor (nAChR) function was assayed using $^{86}Rb^+$ efflux according to a method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Dose-response curves were plotted and the concentration resulting in half maximal activation of specific ion flux through nicotinic receptors determined for human muscle and rat ganglionic preparations (EC50). The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine.

Determination of Interaction with Ganglia:

Ganglionic effects were established on the rat pheochromocytoma clonal line PC12, which is a continuous clonal cell line of neural crest origin derived from a tumor of the rat adrenal medulla expressing ganglionic-type neuronal nicotinic receptors (see Whiting et al., Nature, Vol. 327, pp. 515-518 (1987); Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989); Whiting et al., Mol. Brain Res., Vol. 10, pp. 61-70 (1990)). Discussion concerning the heterogeneity of nicotinic receptors subtypes is set forth in Lukas et al., Internatl. Review Neurobiol., Vol. 34, pp. 25-130 (1992). Acetylcholine nicotinic receptors expressed in rat ganglia share a very high

degree of homology with their human counterparts. See, Fornasari et al., Neurosci. Lett., Vol. 111, pp. 351-356 (1990) and Chini et al., Proc. Natl. Acad. Sci. USA, Vol. 89, pp. 1572-1576 (1992). Both clonal cell lines described above were maintained in proliferative growth phase according to routine protocols (Bencherif et al., Mol. Cell. Neurosci., Vol. 2, pp. 52-65, (1991) and Bencherif et al., J. Pharmacol. Exp. Ther., Vol. 257, pp. 946-953 (1991)). Intact cells on dishes were used for functional studies. Routinely, sample aliquots were reserved for determination of protein concentration using the method of Bradford, Anal. Biochem., Vol. 72, pp. 248-254 (1976) with bovine serum albumin as the standard.

Nicotinic acetylcholine receptor (nAChR) function was assayed using $^{86}Rb^{+}$ efflux according to a method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Cells were plated in 35-mm diameter wells of 6-well dishes for at least 48 hours and loaded for at least 4 hours at 37°C in a medium containing serum, and 1µCi/ml $^{86}Rb^{+}$. Following removal of the loading medium, cells were quickly washed three times with label-free Ringer's solution and exposed for 4 minutes at 20°C to 900 µl of Ringer's containing the indicated concentration of compound to be tested (to define total efflux), or in addition to 100 µM mecamylamine (to define non-specific efflux). The medium was removed and $^{86}Rb^{+}$ was quantitated using Cerenkov detection (see Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988)). Specific ion efflux was determined as the difference in isotope efflux between total and non-specific efflux samples. Dose-response curves were plotted and the concentration resulting in half maximal activation of specific ion flux through nicotinic receptors determined for human muscle and rat ganglionic preparations (EC50). Th maximal activation for individual compounds (Emax) was determined as a

percentage of the maximal activation induced by (S)-(-)-nicotine.

Data are presented in Table I.

Table I

Sample No.	Ki (nM)	logP	Dopamine Release		Muscle Effect	Ganglion Effect
			EC50 (nM)	Emax (%nicotine)	(% nicotine)	(% nicotine)
C-1*	2	0.71	115	100	100	100
1	269	-0.30	4360	113	0	0
2	86	0.04	5800	77	4	1
3	22	1.13	4000	95	0	0
4	58	1.82	8350	87	7	59
5	77	1.39	11339	88	0	0
6	176	1.92	219	60	2	4
7	910	1.51	ND	72	0	31
8 – E-metanicotine	16	1.39	1470	80	15	0

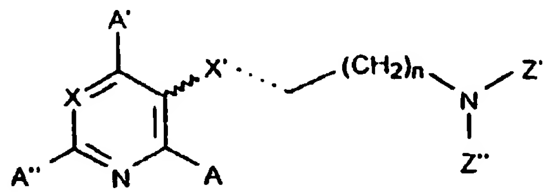
* not an example of the invention

ND = not determined

The data in Table I indicate that the compounds have the capability of passing the blood-brain barrier by virtue of their favorable logP values, binding to high affinity CNS nicotinic receptors as indicated by their low binding constants, and activating CNS nicotinic receptors of a subject and causing neurotransmitter release, thereby demonstrating known nicotinic pharmacology. Thus, the data indicate that such compounds have the capability of being useful in treating CNS disorders involving nicotinic cholinergic systems. Furthermore, the data indicate that the compounds do not cause any appreciable ﬀects at muscle sites and ganglionic sites, thus indicating a lack of undesirable side effects in subjects receiving administration of those compounds.

THAT WHICH IS CLAIMED IS:

1. A method of use of a compound for the manufacture of a medicament for prevention or treatment of a CNS disorder, the compound having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value between about -0.3 and about 0.75; n is an integer which ranges from 1 to 5; Z' and Z'' individually represent hydrogen or alkyl containing one to five carbon atoms; A, A' and A'' individually represent hydrogen, alkyl containing one to seven carbon atoms, or halo; the dashed line in the structure represents a C-C single bond, a C-C double bond or a C-C triple bond; the wavy line in the structure represents a cis (Z) or trans (E) form of the compound when the dashed line is a C-C double bond; and X' represents CH_2 when the dashed line is a C-C single bond, CH when the dashed line is a C-C double bond, and C when the dashed line is a C-C triple bond.

2. A method according to claim 1 whereby the disorder is selected from the group consisting of Tourette's syndrome, attention deficit disorder, and schizophrenia.

3. A method according to claim 1 whereby the disorder is selected from the group consisting of early onset Alzheim r's, senile dementia of the Alzheimer's type, Parkinson's dis ase and Parkinsonism.

4. The method of Claim 2 or 3 whereby the compound is (Z)-metanicotine.

5. The method of Claim 2 or 3 whereby the compound is N-methyl-4-(3-pyridinyl)-3-butyne-1-amine.

6. The method of Claim 2 or 3 whereby the compound is (E)-N-methyl-4-(3-(6-methylpyrindin)yl)-3-butene-1-amine.

7. The method of Claim 2 or 3 whereby the compound is N-methyl-(3-pyridinyl)-butane-1-amine.

8. The method of Claim 2 or 3 whereby the compound is (E)-4-(5-pyrimidinyl)-3-butene-1-amine or (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine.

9. The method of Claim 2 or 3 whereby the compound is (E)-4-(3-(5-methoxypyridin)yl)-3-butene-1-amine or (E)-N-methyl-4-(3-(5-methoxypyrindin)yl)-3-butene-1-amine.

10. The method of Claim 2 whereby the compound is (E)-metanicotine.

11. The method of Claim 2 or 3 whereby X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0; n is an integer which ranges from 1 to 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; and A'' represents hydrogen, methyl or ethyl.

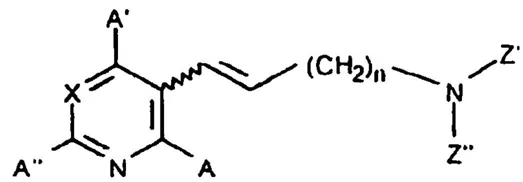
12. The method of Claim 2 or 3 whereby X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value less than 0; n is an integer which ranges from 1 to 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; and A'' represents hydrogen, methyl or ethyl.

13. The method of Claim 2 or 3 whereby n is an integer which ranges from 1 to 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; A'' represents hydrogen, methyl or ethyl; and when the dashed line is a C-C double bond and the compound has the trans (E) form, the substituent species is characterized as having a sigma m value not equal to 0.

14. The method of Claim 2 or 3 whereby X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value between about -0.25 and about 0.6; n is an integer which ranges from 1 to 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; and A'' represents hydrogen, methyl or ethyl.

15. The method of Claim 2 or 3 whereby X is nitrogen; n is an integer which ranges from 1 to 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; and A'' represents hydrogen, methyl or ethyl.

16. A compound having the formula:



where X is nitrogen, CH or C-OCH_3; n is an integer which ranges from 1 to 5; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A, A' and A'' represent hydrogen; and the wavy line represents a cis (Z) or trans (E) form of the compound.

17. The compound of Claim 16 wherein the compound has a trans (E) form.

18. The compound of Claim 16 wherein n is an integer which ranges from 1 to 3.

19. The compound of Claim 16 wherein the compound is selected from the group consisting of (E)-N-methyl-4-[3-(6-methylpyrindin)yl]-3-butenylamine, (E)-N-methyl-4-(5-pyrimidinyl)-3-butene-1-amine, (E)-4-(3-(5-methoxypyridin)yl)-3-butene-1-amine, (E)-N-methyl-4-(3-(5-methoxypyrindin)yl)-3-butene-1-amine, and (E)-4-(5-pyrimidinyl)-3-butene-1-amine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/17034

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/40, 43/54; A61K 31/44, 31/505
US CL :514/343, 256; 544/254; 546/345
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/343, 256; 544/254; 546/345

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,212,188 (CALDWELL ET AL.) 18 May 1993, column 2, lines 20-37, and claims 1-18.	1-19
A	EP, A, 0 377 520 (ELAN CORPORATION P.L.C) 07 November 1990, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
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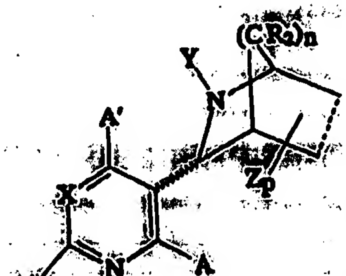
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract



Patients susceptible to or suffering from central nervous system disorders (e.g., neurodegenerative diseases including presenile dementia, senile dementia of the Alzheimer's type, and Parkinsonism including Parkinsons's disease, and other CNS disorders including attention deficit disorder, schizophrenia and Tourette's syndrome) are treated by administering an effective amount of 2-azabicyclo [2.2.1] hept-5-ene and 2-azabicyclo [2.2.2] oct-5-ene compounds. Exemplary compounds are (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, (+/-)-3-exo and (+/-)-3-endo forms of 2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, (+/-)-3-exo and (+/-)-3-endo forms of 2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, (+/-)-3-exo and (+/-)-3-endo forms of 3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene, (+/-)-3-exo and (+/-)-3-endo forms of 3-(3-pyridyl)-2-azabicyclo[2.2.2.]oct-5-ene, (+/-)-3-exo and (+/-)-3-end forms of 2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2.]oct-5-ene, the racemic form of 3-(3-pyridyl)-2-azabicyclo[2.2.2]octane, and the racemic form of 2-methyl-3-(3-pyridyl)-2-azabicycl [2.2.2]octane.

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PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

Background of the Invention

The present invention relates to compounds having pharmaceutical properties, and in particular, to compounds useful for preventing and treating central nervous system (CNS) disorders. The present invention relates to a method for treating patients suffering from or susceptible to such disorders, and in particular, to a method for treating patients suffering from those disorders which are associated with neurotransmitter system dysfunction. The present invention also relates to compositions of matter useful as pharmaceutical compositions in the prevention and treatment of CNS disorders which have been attributed to neurotransmitter system dysfunction.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning, orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a neurotransmitter involved in learning and memory mechanisms). See, Jones, et al., Intern. J. Neurosci., Vol. 50, p. 147 (1990); Perry, Br. Med. Bull., Vol. 42, p. 63 (1986) and Sitaram, et al., Science, Vol. 201, p. 274 (1978). It has been observed that nicotinic acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. See, Giacobini, J. Neurosci. Res., Vol. 27, p. 548 (1990); and Baron, Neurology, Vol. 36, p. 1490 (1986). As such, it would seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Certain attempts have been made to treat SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such receptors upon chronic administration to animals. See, Rowell, Adv. Behav. Biol., Vol. 31, p. 191 (1987); and Marks, J. Pharmacol. Exp. Ther., Vol. 226, p. 817 (1983). It also has been proposed that nicotine can act directly to elicit the release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. See, Rowell, et al., J. Neurochem., Vol. 43, p. 1593 (1984); Sherwood, Human Psychopharm., Vol. 8, pp. 155-184 (1993); Hodges, et al., Bio. of Nic., Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., Br. J. Psych., Vol. 154, p. 797 (1989); and U.S. Patent Nos. 4,965,074 to Leeson and 5,242,935 to Lippiello et al. Other methods for treating SDAT have been proposed, including U.S. Patent Nos. 5,212,188 to Caldwell et al. and 5,227,391 to Caldwell et al. and European Patent Application No. 588,917. Another proposed treatment for SDAT is Cognex, which is a capsule containing tacrine hydrochloride, available from Parke-Davis Division of Warner-Lambert

Company, which reportedly preserves existing acetylcholine levels in patients treated therewith.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. See, Rinne, et al., Brain Res., Vol. 54, pp. 167-170 (1991) and Clark, et al., Br. J. Pharm., Vol. 85, pp. 827-835 (1985). It also has been proposed that nicotine can ameliorate the symptoms of PD. See, Smith et al., Rev. Neurosci., Vol. 3(1), pp. 25-43 (1982).

Certain attempts have been made to treat PD. One proposed treatment for PD is Sinemet CR, which is a sustained-release tablet containing a mixture of carbidopa and levodopa, available from The DuPont Merck Pharmaceutical Co. Another proposed treatment for PD is Eldepryl, which is a tablet containing selefiline hydrochloride, available from Somerset Pharmaceuticals, Inc. Another proposed treatment for PD is Parlodel, which is a tablet containing bromocriptine mesylate, available from Sandoz Pharmaceuticals Corporation. Another method for treating PD and a variety of other neurodegenerative diseases has been proposed in U.S. Patent No. 5,210,076 to Berliner et al.

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of neurological and behavioral symptoms. Typical symptoms include (i) the onset of the disorder before the age of 21 years, (ii) multiple motor and phonic tics although not necessarily concurrently, (iii) variance in the clinical phenomenology of the tics, and (iv) occurrence of quasi daily tics throughout a period of time exceeding a year. Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing; while phonic or vocal tics include throat clearing, sniffling, yelping, tongue clicking and uttering words out of context. The pathophysiology of TS presently is unknown. however it is believed that neurotransmission

dysfunction is implicated with the disorder. See, Calderon-Gonzalez et al., Intern. Pediat., Vol. 8(2), pp. 176-188 (1993) and Oxford Textbook of Medicine, Eds. Weatherall et al., Chapter 21.218 (1987).

It has been proposed that nicotine pharmacology is beneficial in suppressing the symptoms associated with TS. See, Devor et al., The Lancet, Vol. 8670, p. 1046 (1989); Jarvik, British J. of Addiction, Vol. 86, pp. 571-575 (1991); McConville et al., Am. J. Psychiatry, Vol. 148 (6), pp. 793-794 (1991); Newhouse et al., Brit. J. Addic., Vol. 86, pp. 521-526 (1991); McConville et al., Biol. Psychiatry, Vol. 31, pp. 832-840 (1992); and Sanberg et al., Proceedings from Intl. Symp. Nic., S39 (1994). It also has been proposed to treat TS using Haldol, which is haloperidol available from McNeil Pharmaceutical; Catapres, which is clonidine available from Boehringer Ingelheim Pharmaceuticals, Inc., Orap, which is pimozide available from Gate Pharmaceuticals; Prolixin, which is fluphenazine available from Apothecon Division of Bristol-Myers Squibb Co.; and Klonopin, which is clonazepam available from Hoffmann-LaRoche Inc.

Attention deficit disorder (ADD) is a disorder which affects mainly children, although ADD can affect adolescents and adults. See, Vinson, Arch. Fam. Med., Vol. 3(5), pp. 445-451 (1994); Hechtman, J. Psychiatry Neurosci., Vol. 19 (3), pp. 193-201 (1994); Faraone et al., Biol. Psychiatry, Vol. 35(6), pp. 398-402 (1994) and Malone et al., J. Child Neurol., Vol. 9(2), pp. 181-189 (1994). Subjects suffering from the disorder typically have difficulty concentrating, listening, learning and completing tasks; and are restless, fidgety, impulsive and easily distracted. Attention deficit disorder with hyperactivity (ADHD) includes the symptoms of ADD as well as a high level of activity (e.g., restlessness and movement). Attempts to treat ADD have involved administration of Dexedrine, which is a sustained release capsule containing dextroamphetamine sulfate, available from SmithKline Beecham Pharmaceuticals; Ritalin, which is a tablet containing methylphenidate hydrochloride, available from Ciba Pharmaceutical Company; and Cylert, which is a tablet containing premoline, available from Abbott Laboratories. In addition, it has been reported that administration of nicotine to an individual improves that individual's selective and

sustained attention. See, Warburton et al., Cholinergic control of cognitive resources, Neuropsychobiology, Eds. Mendlewicz, et al., pp 43-46 (1993).

Schizophrenia is characterized by psychotic symptoms including delusions, catatonic behavior and prominent hallucinations, and ultimately results in a profound decline in the psychosocial affect of the subject suffering therefrom. Traditionally, schizophrenia has been treated with Klonopin, which is available as a tablet containing clonezepam, available from Hoffmann-LaRoche Inc.; Thorazine, which is available as a tablet containing chlorpromazine, available from SmithKline Beecham Pharmaceuticals; and Clozaril, which is a tablet containing clozapine, available from Sandoz Pharmaceuticals. Such neuroleptics are believed to be effective as a result of interaction thereof with the dopaminergic pathways of the CNS. In addition, a dopaminergic dysfunction possessed by individuals suffering from schizophrenia has been proposed. See, Lieberman et al., Schizophr. Bull., Vol. 19, pp. 371-429 (1993) and Glassman, Amer. J. Psychiatry, Vol. 150, pp. 546-553 (1993). Nicotine has been proposed as being effective in affecting neurotransmitter disfunction associated with schizophrenia. See, Merriam et al., Psychiatr. Annals, Vol. 23, pp. 171-178 (1993) and Adler et al., Biol. Psychiatry, Vol. 32, pp. 607-616 (1992).

Nicotine has been proposed to have a number of pharmacological effects. Certain of those effects may be related to effects upon neurotransmitter release. See, for example, Sjak-shie et al., Brain Res., Vol. 624, pp. 295-298 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported by Rowell et al., J. Neurochem., Vol. 43, pp. 1593-1598 (1984); Rapier et al., J. Neurochem., Vol. 50, pp. 1123-1130 (1988); Sandor et al., Brain Res., Vol. 567, pp. 313-316 (1991) and Vizi, Br. J. Pharmacol., Vol. 47, pp. 765-777 (1973). Release of norepinephrine by neurons upon administration of nicotine has been reported by Hall et al., Biochem. Pharmacol., Vol. 21, pp. 1829-1838 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., Arch. Int. Pharmacodyn. Ther., Vol. 296, pp. 91-97 (1977). Release of glutamate by neurons upon administration of nicotine has been reported by Toth et al., Neurochem Res., Vol. 17, pp. 265-271 (1992).

Therefore, it would be desirable to provide a pharmaceutical composition containing an active ingredient having nicotinic pharmacology, which pharmaceutical composition is capable of eliciting neurotransmitter release within a subject in order to prevent or treat a neurological disorder. In addition, nicotine reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used for the treatment of certain CNS disorders. See, Sanberg et al., Pharmacol. Biochem. & Behavior, Vol. 46, pp. 303-307 (1993); Harsing et al., J. Neurochem., Vol. 59, pp. 48-54 (1993) and Hughes, Proceedings from Intl. Symp. Nic., S40 (1994). Furthermore, various other beneficial pharmacological effects of nicotine have been proposed. See, Decina et al., Biol. Psychiatry, Vol. 28, pp. 502-508 (1990); Wagner et al., Pharmacopsychiatry, Vol. 21, pp. 301-303 (1988); Pomerleau et al., Addictive Behaviors, Vol. 9, p. 265 (1984); Onaivi et al., Life Sci., Vol. 54(3), pp. 193-202 (1994) and Hamon, Trends in Pharmacol. Res., Vol. 15, pp. 36-39.

It would be desirable to provide a useful method for the prevention and treatment of a CNS disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a disorder. It would be highly beneficial to provide individuals suffering from certain CNS disorders with interruption of the symptoms of those diseases by the administration of a pharmaceutical composition which has nicotinic pharmacology and which has a beneficial effect upon the functioning of the CNS, but which does not provide any significant associated side effects (e.g., increased heart rate and blood pressure) attendant with interaction of that compound with cardiovascular sites. It would be highly desirable to provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors which have the potential to affect the functioning of the CNS, but which does not significantly affect those receptors which have the potential to induce undesirable side effects (e.g., appreciable pressor cardiovascular effects and appreciable activity at skeletal muscle sites).

Summary of the Invention

The present invention, in one aspect, relates to 2-azabicyclo[2.2.1]hept-5-ene compounds. Such compounds have a bicyclic functionality; and (i) the bridge of such functionality has a length of 1 carbon atom, (ii) the bicyclic functionality can have a C-C single bond or a C-C double bond positioned at its 5-6 position, and (iii) the nitrogen of the bicyclic functionality can possess a substituent group other than hydrogen, and (iv) the 3 position of the bicyclic functionality can possess a substituent positioned such that the compound can exist in either an endo or exo form.

The present invention, in another aspect, relates to 2-azabicyclo[2.2.2]oct-5-ene compounds. Such compounds have a bicyclic functionality; and (i) the bridge of such functionality has a length 2 carbon atoms, (ii) the bicyclic functionality can have a C-C single bond or a C-C double bond positioned at its 5-6 position, and (iii) the nitrogen of the bicyclic functionality can possess a substituent group other than hydrogen, and (iv) except when a C-C single bond exists at the 5-6 position of the bicyclic functionality, the 3 position of the bicyclic functionality can possess a substituent positioned such that the compound can exist in either an endo or exo form.

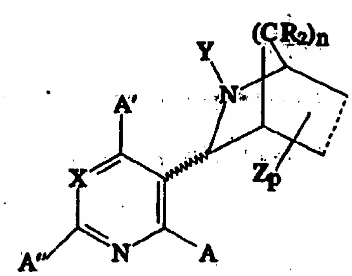
The present invention relates to a method for providing prevention or treatment of a central nervous system (CNS) disorder. The method involves administering to a subject an effective amount of a compound of the present invention. The compound can be administered in a free base form or in the form of a pharmaceutically acceptable salt. The compound can be administered in the form of a racemic mixture or as an enantiomer.

The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a compound of the present invention. Such a pharmaceutical composition incorporates a compound which has the capability of interacting with relevant nicotinic receptor sites of a subject, and hence has the capability of acting as a therapeutic in the prevention or treatment of a CNS disorder. The compound can have a free base form or be in the form of a pharmaceutically acceptable salt. The compound can be administered in the form of a racemic mixture or as an enantiomer.

The pharmaceutical compositions of the present invention are useful for the prevention and treatment of CNS disorders. The pharmaceutical compositions provide therapeutic benefit to individuals suffering from certain CNS disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions have the potential to (i) exhibit nicotinic pharmacology and affect nicotinic receptors sites in the CNS (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) not provide appreciable adverse side effects (e.g., significant increases in blood pressure and heart rate, and significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of CNS disorders.

Detailed Description of the Preferred Embodiments

The present invention relates to certain compounds having the formula:

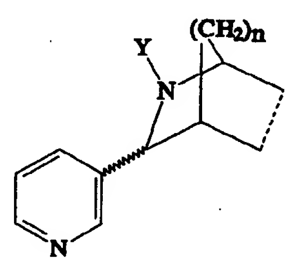


where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0;

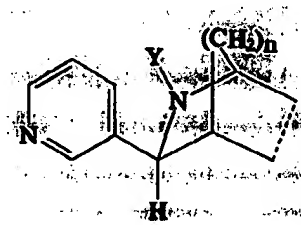
as determined in accordance with Hansch et al., Chem. Rev., Vol. 91, pp. 165-195 (1991); n is an integer which can range from 1 to 2; R individually represents hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, such as methyl, ethyl or isopropyl), and preferably all R are hydrogen; Z represents lower alkyl (e.g., alkyl containing one to five carbon atoms, such as methyl, ethyl or isopropyl); A, A' and A'' individually represent hydrogen, alkyl (e.g., lower straight chain or branched alkyl, including C_1 - C_7, but preferably methyl or ethyl), or halo (e.g., F, Cl, Br or I), and A'' can represent an aromatic group-containing species, such as aryl, phenyl, pyridyl, arylalkyl (e.g., where the alkyl substituent contains 1 to 4 carbon atoms, and an exemplary arylalkyl species is benzyl) or pyrimidyl; the dashed line in the structure represents a C-C single bond or a C-C double bond; the wavy line in the structure indicates that the compound can have a 3-endo or 3-exo form; and p is an integer ranging from 0 to 7 when the dashed line is a C-C single bond, and an integer ranging from 0 to 5 when the dashed line is a C-C double bond. Preferably, p is 0 or 1, and most preferably p is 0. Y represents hydrogen, alkyl (e.g., alkyl containing 1 to 7 carbon atoms), or an aromatic group-containing species, such as aryl, phenyl, pyridyl, arylalkyl (e.g., where the alkyl substituent contains 1 to 4 carbon atoms, and an exemplary arylalkyl species is benzyl) or pyrimidyl. Preferably Y is straight chain or branched alkyl containing 1 to about 4 carbon atoms (e.g., methyl or ethyl). X includes N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'', $C-CF_3$, C-OH, C-CN, C-SH, $C-SCH_3$, $C-N_3$, $C-SO_2CH_3$, C-OR', C-C(=O)N R'R'', C-NR'C(=O)R', C-C(=O)OR', C-OC(=O)R', C-OC(=O)NR'R'', C-NR'C(=O)OR', and C-Ph, where R' and R'' are individually hydrogen or lower alkyl (e.g., alkyl containing one to five carbon atoms, preferably methyl or ethyl), and Ph is an aromatic group-containing species, such as aryl, phenyl, pyridyl, arylalkyl (e.g., where the alkyl substituent contains 1 to 4 carbon atoms, and an exemplary arylalkyl species is benzyl) or pyrimidyl. When X represents a carbon atom bonded to a substituent species, that substituent species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In addition, it is highly preferred that A is hydrogen, it is preferred that A' is hydrogen, and normally A'' is hydrogen. Generally, both A and A' are

hydrogen; sometimes A and A' are hydrogen, and A'' is chloro, methyl or ethyl; and often A, A' and A'' are all hydrogen. For certain preferred compounds, the dashed line is a C-C double bond, and Y is a substituent other than hydrogen (e.g., alkyl containing 1 to 4 carbon atoms). For certain preferred compounds, the dashed line is a C-C single bond, and Y is hydrogen. Representative compounds include (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene for which X is C-Br, A, A', A'', R are H, n is 1, p is 0, Y is CH_3, and the dashed line represents a C-C double bond. Other representative compounds include (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene for which X is CH, A'' is CH_3, A, A', R are H, n is 1, p is 0, Y is CH_3, and the dashed line represents a C-C double bond.

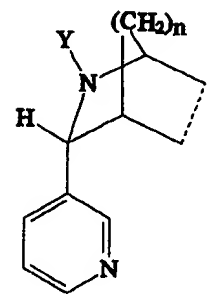
Of particular interest are compounds having the formula:



where Y, n and the dashed line are as defined hereinbefore, and those compounds can have the endo or exo form. The exo form is:



and the endo form is:



Representative compounds include (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, for which the dashed line is a C-C double bond, Y is $-CH_3$ and n is 1. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, for which the dashed line is a C-C double bond, Y is $-CH_2-CH_3$ and n is 1. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, for which the dashed line is a C-C double bond, Y is $-CH_2C_6H_5$ and n is 1. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene, for which the dashed line is a C-C double bond, Y is $-CH_2$-para-methoxyphenyl and n is 1. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene, for which the dashed line is a C-C double bond, Y is H and n is 2. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene, for which the dashed line is a C-C double bond, Y is H and n is 2. Other representative compounds are (+/-)-3-exo and (+/-)-3-endo forms of 2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene, for which the dashed line is a C-C double bond, Y is $-CH_3$ and n is 2. Another representative compound is the racemic form of 3-(3-pyridyl)-2-azabicyclo[2.2.2]octane, for which the dashed line is a C-C single bond, Y is H and n is 2. Another representative compound is the racemic form of 2-methyl-3-

(3-pyridyl)-2-azabicyclo[2.2.2]octane, for which the dashed line is a C-C single bond, Y is $-CH_3$ and n is 2.

Compounds of the present invention can be synthetically produced in a step-wise fashion. Pyridyl 3-carboxaldehydes and pyrimidyl 3-carboxaldehydes are provided. Compounds such as 4-methyl-3-pyridinecarboxaldehyde, 5-methyl-3-pyridinecarboxaldehyde, 4-phenyl-3-pyridinecarboxaldehyde, 5-phenyl-3-pyridinecarboxaldehyde, 6-phenyl-3-pyridinecarboxaldehyde, 4-chloro-3-pyridinecarboxaldehyde and 5-chloro-3-pyridinecarboxaldehyde can be prepared in accordance with the types of procedures set forth in Comins et al, <u>Heterocycles</u>, Vol. 26, p. 2159 (1987). Compounds such a 2-methyl-3-pyridinecarboxaldehyde and 6-methyl-3-pyridinecarboxaldehyde can be provided from the corresponding substituted nicotinic acids using the types of techniques described in Swern et al, <u>J. Org. Chem.</u>, Vol. 31, p. 4226 (1966). Compounds such as 6-chloro-3-pyridinecarboxaldehyde and 6-bromo-3-pyridinecarboxaldehyde can be prepared in accordance with the techniques described by Windscheif et al, <u>Synthesis</u>, p. 87 (1994). Compounds such as 4-bromo-3-pyridinecarboxaldehyde can be obtained by regiospecific lithiation of nicotinaldehyde followed by lithium/halogen exchange as reported by Kelly et al, <u>Tetrahedron Letters</u>, Vol. 34, p. 6173 (1993). Compounds such as 2-chloro-3-pyridinecarboxaldehyde can be prepared by reduction of 2-chloro-3-cyanopyridine by Raney Nickel and formic acid as reported by Lynch et al, <u>Can. J. Chem.</u>, Vol. 66, p. 420 (1988). Compounds such as 2-bromo-3-pyridinecarboxaldehyde can be provided by direct ortho metalation of 2-bromopyridine followed by formylation with N,N-dimethyl formamide as set forth by Melnyk et al, <u>Synth. Commun.</u>, Vol. 23, p. 2727 (1993). See, also, Rondahl, L., Acta. Pharm., Vol. 14, p. 113 (1977).

Pyridyl 3-carboxaldehydes and pyrimidyl 3-carboxaldehydes then each are converted to the appropriate Shiff base using techniques which are familiar to those skilled in the art of organic synthesis. Then, racemic mixtures of compounds of the present invention are provided by Diels Alder reaction with an appropriate cyclopentadiene.

Alternately, pyridyl 3-carboxaldehydes and pyrimidyl 3-carboxaldehydes are converted to their corresponding bis-carbamates using techniques which are familiar to those skilled in the art of organic synthesis. Then, racemic mixtures of compounds of the present invention are provided by Diels Alder reaction with an appropriate cyclohexadiene.

Compounds of the present invention can be provided as mixtures of (+/-)-3-exo and (+/-)-3-endo isomers, and the mixtures can be separated into the (+/-)-3-exo form and the (+/-)-3-endo form using column chromatography techniques. For example, (+/-)-exo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene is prepared from a mixture of isomers at a yield of 20% using silica gel chromatography (200-400 mesh), eluting with 5% of methanol in chloroform as eluent, and such isomer has a migration value (R_f) of 0.41 when analyzed by thin layer chromatography, using a solvent system of chloroform-methanol (90:10,v/v). The corresponding (+/-)-endo-isomer is similarly obtained using a silica gel chromatography and has R_f=0.62. (+/-)-3-Exo-2-(p-methoxybenzyl)-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene is prepared from a mixture of isomers at a yield of 14% using silica gel chromatography (200-400 mesh), eluting with 3% of methanol in chloroform as eluent, and such isomer has R_f=0.48 when analyzed by thin layer chromatography, using a solvent system of methanol-chloroform (5:95, (v/v). The corresponding (+/-)-endo-isomer is similarly obtained using silica gel chromatography and has R_f=0.60. (+/-)-3-Exo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene is prepared from a mixture of isomers at a yield of 13% using a silica gel chromatography (200-400 mesh), eluting with 5% of methanol in chloroform as eluent, and such isomer has R_f=0.38 when analyzed by thin layer chromatography, using a solvent system of methanol-chloroform (5:95, v/v). The corresponding (+/-)-endo isomer is similarly obtained using a silica gel chromatography and has R_f=0.52. (+/-)-3-Exo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene is prepared from a mixture of isomers at a yield of 23% using silica gel chromatography (200-400 mesh, 60 Å), eluting with acetonitrile in chloroform (1:6. v/v) as eluent, and such isomer has R_f=0.41 when analyzed by thin layer chromatography, using a solvent system of

methanol-chloroform (1:6, v/v). The corresponding (+/-)-endo isomer is similarly obtained using a silica gel chromatography and has R_f=0.45.

Racemic mixtures are provided, and the compounds of the present invention can be provided as enantiomers via chromatographic separation. Enantiomeric resolution of racemic compounds can be achieved by high performance liquid chromatography using beta-cyclodextrin bonded silica gel as the chiral stationary phase based on the method developed for nicotine and nornicotine analogs. See, Armstrong et al., Anal. Chem., Vol. 60, p. 2120-2127 (1988).

Representative compounds of the present invention are (+/-)-3-endo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene and(+/-)-3-exo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene which are prepared essentially in accordance with the following techniques. Ethyl-6-methyl-3-pyridinecarboxylate is prepared essentially in accordance with the techniques described by E. Leete et al, Phytochemistry, Vol.10, p. 2687 (1971) to afford 5g (83%) of that compound. 6-Methyl-3-pyridinemethylalcohol is prepared essentially in accordance with the techniques described in Nutaitis et al, Org. Prep. Proc. Int., Vol. 24, pp.143-146 (1992) to afford 2.9 g (78%) of that compound. Dimethyl sulfoxide (3.50 mL, 44 mmol) is added dropwise at -60°C, over a period of 5 min., to a solution of oxalyl chloride (2 mL. 22 mmol) in dry methylene chloride (50 mL). The reaction mixture is stirred at -60°C for 2 min., then a solution of 6-methyl-3-pyridinemethylalcohol (2.5 g, 20.32 mmol) in dry methylene chloride (5 mL) is added over a 15 min. period and the resulting solution is stirred for 15 min. at -60°C. Triethylamine (15mL) is added and the solution is stirred for 5 additional minutes, followed by the addition of water (100mL). The reaction mixture is allowed to warm to room temperature and extracted with chloroform (4x25 mL). The organic extracts are dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator to give 2.5g of a thick syrup. The pure compound, 6-methyl-3-pyridinecarboxaldehyde, (2.09, 85%) is obtained after column chromatography over silica gel (200-400 mesh) using chloroform-methanol (98:2, v/v) as eluent. A mixture of 6-methyl-3-pyridinecarboxaldehyde (2.5g, 20.66mmol), methylamine (12mL, 2.0 M solution

in tetrahydrofuran) and molecular sieves (3Å, 5.0 g) are stirred for 12 hours under a nitrogen atmosphere. The reaction mixture is then filtered through celite. Concentration of the resulting solution on a rotary evaporator yields the Schiff base, N-[3-(6-methylpyridylidene)]methylamine, (2.6g, 95%) which is used immediately in the next step without further purification. A solution of N-[3-(6-methylpyridylidene)]methylamine (1.8 g, 13.43 mmol) in dry methylene chloride (10 mL, freshly distilled over P_2O_5) is stirred for 30 min. with powdered 3Å molecular sieves (5g) under nitrogen. Titanium chloride (1.46 mL, 13.43 mmol) then is added, and the resulting mixture stirred for an additional 30 min. The mixture is cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (2.4 mL, 26.9 mmol) in dry methylene chloride (5 mL).The reaction mixture is allowed to warm to ambient temperature overnight. Chloroform (10 mL) is added to the mixture, and the solution is filtered through a bed of Celite. The filtrate is evaporated to dryness and the resulting residue is dissolved by addition of a 10% aqueous solution of sodium hydroxide. The resulting solution is stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts are dried over anhydrous K_2CO_3, filtered, and evaporated to give 2.0g of a crude brown syrup which is shown by ^{1}H NMR to be a mixture of <u>endo</u>-and <u>exo</u>-isomers (ratio 65:35, respectively). For (+/-)-<u>endo</u>-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene, R_f=0.48, and the isomer is obtained by column chromatography (solvent system: methanol-chloroform (10:90, v/v)). For (+/-)-exo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene, R_f=0.42, and the isomer is obtained by column chromatography (solvent system: methanol-chloroform (10:90, v/v)).

The present invention relates to a method for providing prevention of a CNS disorder to a subject susceptible to such a disorder, and for providing treatment to a subject suffering from a CNS disorder. In particular, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of the CNS disorder (i.e., provide protective effects), amelioration of the symptoms of the CNS disorder, and amelioration of the reoccurrence of the CNS disorder. The method involves administering an effective amount of a compound selected from the general

formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. The majority of the compounds have either an endo or exo isomeric form. The compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts, such as chloride, perchlorate, ascorbate, sulfate, tartrate, fumarate, citrate, malate, lactate or aspartate salts). CNS disorders which can be treated in accordance with the present invention include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics, steroids and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular CNS disorder. As such, the pharmaceutical compositions can be formulated to provide the desired formulation.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al.); topically (e.g., in lotion form); rally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid

carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); or transdermally (e.g., using a transdermal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Ciba-Geigy Corporation and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, such as a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that affect the functioning of the CNS.

The dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By 'effective amount', 'therapeutic amount' or 'effective dose' is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder. Thus, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to elicit neuropharmacological effects (e.g., elicit neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than 0, often are greater than about 1, and frequently are greater than about 1.5. The log P values of such typical compounds generally are less than about 4, often are less than about 3.5, and frequently are less than about 3. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and in most circumstances, cause activation of, nicotinic cholinergic receptors of the brain of the patient. As such, such compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of preferred compounds useful in carrying out the present invention generally exceed about 1 nM, often exceed about 200 nM, and frequently exceed about 500 nM. The receptor binding constants of such preferred compounds generally are less than about 10 uM, often are less than about 7 uM, and frequently are less than about 2 uM. Receptor binding constants provide a measure of the ability of the

compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See. Cheng, et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively eliciting neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, such compounds have the ability to cause relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, certain compounds useful in carrying out the present invention provide for the secretion of dopamine in amounts of at least about 10 percent, often at least about 20 percent, and frequently at least about 30 percent, of that elicited by an equal molar amount of S(-) nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from muscle preparations. Generally, preferred compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability f those compounds to activate nicotinic function of adrenal chromaffin tissue. As such, such compounds have

poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, preferred compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 15 percent, often by less than 10 percent, and frequently by less than 5 percent, of that elicited by an equal molar amount of (S)-(-)-nicotine.

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the reoccurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as demonstrated by increased effects relating to the cardiovascular system, and effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/5, often less than 1/10, and even less than 1/100, that amount sufficient to cause any side effects to a significant degree.

The following example is provided in order to further illustrate various embodiments of the invention but should not be construed as limiting the scope thereof. Unless otherwise noted, all parts and percentages are by weight.

EXAMPLE

Sample No. 1 is (+/-)-endo 3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate which is prepared essentially in accordance with the following techniques.

N-N'-carboethoxy-(3-pyridyl)-diaminomethane (I)

This compound was prepared as reported by P.Quan et al., J. Org. Chem., Vol. 30, pp. 269 (1965) and afforded 10g (55%) of compound (I). Mp= 163°-165°C.

(+/-)-Endo and (+/-)-exo 3-(3-pyridyl)-2-carboethoxy-2-azabicyclo[2.2.2]oct-5-ene (II).

A solution of compound (I) (4.0g , 14.8 mmole), 1,3-cyclohexadiene (1.48 mL, 16.28 mmole), and boron trifluoride acetic acid complex (16.8mL, 121.65mmole) in glacial acetic acid (30 mL) was heated for 3 hours at 70°C. A solution of 40% (w/v) of NaOH in water was added to the reaction mixture. which was then extracted with chloroform (4x25 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered and concentrated on a rotary evaporator. The resulting thick syrup was purified by column chromatography over silica gel (200-400 mesh) using acetonitrile in chloroform (1:7, v/v) as eluant and afforded 2.60 g (67%) of a mixture of (+/-)-endo and (+/-)-exo isomers (ratio 60:40, respectively). This mixture was used in the next step without separation of the isomers.

^{1}H NMR of the mixture ($CDCl_3$): δ 8.44 (m, 2 H), 7.46 (m, 1H), 7.21 (m, 1H), 6.36 and 6.22 (2x m, 1H), 5.62 and 5.49 (2xm, 1H), 4.1 and 3.96 (2xm, 2H), 2.76, 2.62 and 2.55 (3xm, 3H), 2.42 and 2.35 (2xm, 1H), 2.08 and 1.86 (2xm, 1H), 1.5 (m, 1H), 1.47 (m, 1H), 1.24, 0.92 and 0.84 (3xt, 3H).

(+/-)-Endo- and (+/-)-exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (III).

Compound (II) (a mixture of endo and exo isomers) (1.5g, 58.13 mmol) was dissolved in a 20% (w/v) solution of NaOH in absolute ethanol (20 mL) and the mixture refluxed for 24 hours. The organic solvent was then evaporated on a rotary evaporator. The pH of the basic residue was adjusted to 9 by addition of a solution of 2N HCl in water and the aqueous mixture was extracted with ethyl acetate (4x10 mL). The organic extracts were dried over anhydrous K_2CO_3, concentrated, filtered and the solvent evaporated. The thick syrup obtained was chromatographed over silica gel (200-400 mesh). Both (+/-)- endo and (+/-)- exo isomers were isolated in the pure form by silica gel chromatography by eluting with 10% of methanol in chloroform.

(+/-)-Endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (IV).

Compound (IV) with a R_f value of 0.6 (solvent system chloroform:methanol (9:1, v/v)) was isolated from silica gel column chromatography to afforded 520mg (48%) of pure (+/-)- endo-isomer.

^{1}H NMR ($CDCl_3$): δ 8.52 (d, 1H), 8.41-8.32 (m, 1H), 7.70-7.60 (m, 1H), 7.20-7.10 (m, 1H), 6.01-5.90 (m, 1H), 5.60-5.50 (m, 1H), 4.10 (s, 1H), 3.62 (t, 1H), 2.80 (br s, 1H NH), 2.50-2.36 (m, 1H), 2.33-2.28 (m, 1H), 2.20-2.12 (m, 1H), 2.02-1.92 (m, 1H), 1.70 (d, 1H).

(+/-)-Endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate(V).

To a solution of compound (IV) (100mg, 0.537mmol) in absolute ethanol (5 mL) was added fumaric acid (124mg, 1.068 mmol). The resulting suspension was sonicated until complete dissolution occured. The solvent was removed on a rotary evaporator to afford a colorless syrup which was crystallized from absolute ethanol to yield 179mg (79%) of compound (V). Mp=165°-167°C.

^{1}H NMR (D2O + TSP): δ 8.75 (s, 1H), 8.69 (d, 1H), 8.38 (m, 1H), 7.30 (m1H), 6.68 (s, 4H), 5.56 (s, 2H), 4.92 (s, 1H), 4.32 (m, 1H), 3.12 (s, 1H), 2.72-2.12 (m, 1H), 2.50-2.38 (m, 2H), 2.30 (d, 1H)

Sample No. 2 is (+/-)-exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate which is prepared essentially in accordance with the following techniques.

(+/-)-Exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (VI).

The (+/-)- exo-isomer R_f=0.45 (solvent system: chloroform:methanol (9:1, v/v)) is isolated after column chromatography of the crude endo-exo mixture (III) over silica gel (200-400 mesh) to afford 330mg (30%) of the isomerically pure product.

^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 8.42 (m, 1H), 7.82-7.78 (m, 1H), 7.26-7.15 (m, 1H), 6.16-6.04 (m. 1H), 5.48-5.38 (m, 1H). 4.72 (d, 1H), 3.61 (t. 1H,), 2.72 (d, 1H,), 2.60 (s. NH). 2.20-2.00 (m. 3H), 1.50-1.40 (m, 1H).

(+/-)-Exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate (VII)

To a solution of compound (VI) (100mg,0.537mmol) in absolute ethanol (5 mL) was added fumaric acid (124mg,1.068.mmol). The resulting suspension was

sonicated until complete dissolution occured. The solvent was removed on a rotary evaporator to give a colorless syrup which was crystallized from absolute ethanol to yield 165mg (74%) of compound (VII). Mp=167°-169° C.

^{1}H NMR (D_2O & TSP): δ 9.00-8.50 (brs, 2H), 8.14-8.08 (dd, 1H), 7.70 (brs, 1H), 6.60 (s, 2H), 6.00-5.88 (m, 2H), 4.80 (s, 1H), 4.20 (t, 1H), 3.00-2.95 (m, 1H), 2.62-2.45 (dd, 1H), 2.40-2.21 (m, 2H), 2.20-2.16 (d, 1H).

Sample No. 3 is (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate which is prepared essentially in accordance with the following techniques.

(+/-)-Endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (VIII).

Formic acid (5 mL, 95-97 %) and formaldehyde (0.5 mL, 37% in water) were added to (+/-)- endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (IV) (170 mg,0. 913mmol) and the mixture refluxed for 24 hours under nitrogen. The reaction mixture was cooled to 0°C (ice bath), basified with a 40% (w/v) aqueous solution of NaOH (pH=9) and extracted with chloroform (4x10 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered and concentrated. The resulting oily residue was distilled under reduced pressure (97°-98° C/ 0.4 mm Hg) to give 170mg (93%) of (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2] oct-5-ene (VIII).

^{1}H NMR ($CDCl_3$): δ 8.60 (d, 1H), 8.50 (dd, 1H), 7.80-7.55 (m. 1H), 7.30 7.20 (m, 1H), 6.02-5.92 (m, 1H), 6.34-6.28 (m, 1H), 3.45 (t, 1H), 3.16 (s, 1H), 2.42-2.40 (m, 1H), 2.38 (s, 3H), 2.30 (m, 1H), 2.28-2.12 (m, 3H), 1.62 (d, 1H).

(+/-)-Endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate (IX).

To a solution of compound (VIII) (100mg, 0.54mmol) in absolute ethanol (5 mL) was added fumaric acid (124mg, 1.08 mmol). The resulting suspension was sonicated until complete dissolution occured. The solvent was removed on a rotary evaporator to give a colorless syrup which was crystallized from absolute ethanol to yield 190mg (85%) of compound (IX). Mp=143°-144°C.

^{1}H NMR (D2O+ TSP): δ 8.70-8. 60 (m, 2H), 8.20-8.12 (m, 1H), 7.71-7.15 (m, 1H), 6.60 (s, 4H), 6.15-6.10 (m, 1H), 5.90-5.82 (m, 1H), 4.32 (s, 1H), 4.11 (t, 1H), 2.97-2.90 (m, 1H), 2.79 (s, 3H), 2.59-2.40 (m, 2H), 2.38-2.20 (m, 2H).

Sample No. 4 is (+/-)-Exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate which is prepared essentially in accordance with the following techniques.

(+/-)-Exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (X).

Formic acid (5 mL, 95-97 %) and formaldehyde (0.5 mL, 37% in water) were added to (+/-)-exo 3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (VI) (150 mg, 0.75mmol) and the mixture refluxed for 24 hours under nitrogen. The reaction mixture was cooled to 0°C (ice bath), basified with a 40% (w/v) aqueous solution of NaOH (pH= 9) and extracted with chloroform (4x10 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered and concentrated. The resulting oily residue was distilled under reduced pressure (107°-108° C/ 0.4 mm Hg) to give 145mg (97%) of (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2] oct-5-ene (X).

(+/-)-Exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene fumarate (XI).

To a solution of compound (X) (50mg, 0.25mmol) in absolute ethanol (5 mL) was added fumaric acid (62mg, 0.5 mmol). The resulting suspension was sonicated until complete dissolution occured. The solvent was removed on a rotary evaporator to afford a colorless syrup which was crystallized from absolute ethanol to yield 80mg (74%) of compound (XI). Mp=147°-148°C.

^{1}H NMR (D2O+ TSP): δ 8.67-8.65 (d, 1H), 8.56 (s, 1H), 8.11-8.02 (dd, 1H), 7.87-7.69 (m, 1H), 6.62 (s, 4H), 6.20-6.00 (m, 2H), 4.90-4.82 (d, 1H), 4.08-3.98 (t, 1H), 2.90 (m, 2H), 2.60-2.50 (m, 1H), 2.40-2.20 (m, 2H), 1.90-1.73 (d, 1H).

Sample No. 5 is (+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane fumarate which was prepared essentially in accordance with the following techniques.

(+/-)-3-(3-pyridyl)-2-carboethoxy-2-azabicyclo[2.2.2]octane (XII).

A solution of the (+/-)-endo and (+/-)-exo isomers of 3-(3-pyridyl)-2-carboethoxy-2-azabicyclo[2.2.2]oct-5-ene. compound (II), (750 mg, 2.90 mmol) in glacial acetic acid (0.5mL) and Pd/C (10 %) was shaken under a H_2 atmosphere in a Parr apparatus for 2 hours. The catalyst was removed by filteration over a bed of Celite and the filterate was basified by addition of a

solution of 40% of NaOH in water. The aqueous basic solution was extracted with dichloromethane (4x20 mL) to give 740 mg (98%) of compound (XII).

^{1}H NMR ($CDCl_3$): δ 8.48 (m, 2H), 7.60 (m. 2H), 4.78 and 4.67 (m,1H), 4.30 (m, 1H), 4.13 and 4.10 (q, 2H), 2.19 (m, 2H), 1.90 (m, 3H), 1.63 (m, 4H,), 1.28 and 0.90 (t, 3H).

(+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane (XIII).

(+/-)-3-(3-pyridyl)-2-carboethoxy-2-azabicyclo[2.2.2]octane (XII) (500 mg, 1.92 mmol) was dissolved in a solution of 20% (w/v) NaOH in absolute ethanol (10 mL) and refluxed for 24 h. The organic solvent was evaporated on a rotary evaporator. The pH of the basic residue was adjusted to 9 by addition of a solution of 2N HCl in water and was extracted with ethyl acetate (4x10 mL). The organic extracts were dried over anhydrous K_2CO_3 and concentrated. The resulting oily residue was purified by distillation under reduced pressure (108°-110° C / 0.4 mm Hg) to afford 300mg (83%) of compound (XIII).

^{1}H NMR ($CDCl_3$): δ 8.62-8.61 (d, 1H), 8.44-8.41 (m, 1H), 7.80-7.72 (m, 1H), 7.24-7.21 (m, 1H), 4.30 (s, 1H), 3.71-3.63 (m, 1H), 2.20 (m, 1H), 2.0-1.51 (m, 8H), 1.42 (d, 1H).

(+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane fumarate (XIV).

To a solution of compound (XIII) (100mg,0.531mmol) in absolute ethanol (5 mL) was added fumaric acid (124mg, 1.062mmol). The resulting suspension was sonicated until complete dissolution occurred. The solvent was removed on rotary evaporator to give a colorless syrup which was crystallized from absolute ethanol to yield 156mg (70%) of compound (XIV). Mp=180°C (decomposition).

^{1}H NMR (D_2O, TSP): δ 8.80 (br s, 2H), 8.40 (d, 1H), 7.95 (s, 1H), 6.70 (s, 2H), 5.08 (s, 1H), 4.21 (s, 1H), 3.08 (s, 1H), 2.40 (m, 1H), 2.02-1.60 (m, 8H).

Sample No. 6 is (+/-)-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane fumarate which was prepared essentially in accordance with the following techniques.

(±)-2-Methyl-3-(3-pyridyl)-2-azabicylo[2.2.2]octane (XV).

F rmic acid (5 mL, 95-97 %) and formaldehyde (0.5 mL, 37 %) were added to 3-(3-pyridyl)-2-azabicylo[2.2.2]octane (XIII) (170 mg) and refluxed for 24 hours

under N_2. The reaction mixture was cooled to 0°C (ice bath), basified by addition of a solution of 40 % w/v NaOH in water (pH=9) and extracted with chloroform (4x10 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered and concentrated. The resulting oil was purified by distillation under reduced pressure (116°-118°C/0.4 mm Hg) to give 160mg (88%) of (+/-)-2-methyl-3-(3-pyridyl)-2-azabicylo[2.2.2]octane (XV).

^{1}H NMR ($CDCl_3$):δ 8.85 (s, 1H), 8.80-8.10 (d, 1H), 7.78-7.71 (m, 1H), 7.23-7.20 (m, 1H),4.70 (s, 1H), 3.60 (s, 1H), 2.5 (s, 3H), 2.25 (s, 1H), 2.20-1.95 (m, 2H), 1.80-1.69 (m, 3H), 1.50-1.42 (m, 3H).

(+/-)-2-Methyl-3-(3-pyridyl)-2-azabicylo[2.2.2]octane fumarate (XVI)

To a solution of compound (XV) (120mg, 0.495mmol) in absolute ethanol (5 mL) was added fumaric acid (138mg, 1.18 mmol). The resulting suspension was sonicated until complete dissolution occurred. The solvent was removed on a rotary evaporator to give a colorless syrup which was crystallized from absolute ethanol to yield 190mg (88%) of compound (XVI). Mp=142°-143°C.

^{1}H NMR (D_2O + TSP): δ 8.71 (s, 1H), 8.64-8.62 (m, 1H), 8.30-8.22 (d, 1H), 7.79-7.72 (m, 1H), 6.60 (s, 3H), 4.58 (s, 1H), 3.90 (s, 1H), 2.90 (s, 3H), 2.80(s, 1H), 2.46-2.38 (m, 1H), 2.10-1.95 (d, 2H), 1.92-1.62 (m, 5H).

Sample No. 7 is (+/-)-endo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

N-(3-pyridylidene)-ethylamine (XVII).

A solution of 3-pyridinecarboxaldehyde (1g, 9.3 mmol) and ethylamine (661mg, 10.2 mmol, 70% wt in water) was stirred at room temperature for 18h. The reaction mixture was diluted with chloroform (20 mL) and dried over anhydrous K_2CO_3. The solution was filtered and the solvent was evaporated to afford N-(3-pyridylidene)-ethylamine (XVII) 1.15g (92%), which was used immediately without further purification.

^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.60 (d, 1H), 8.28 (s,1H), 8.10 (m, 1H), 7.4-7.3 (m, 1H), 3.78-3.62 (q, 2H), 1.38-1.22 (t, 3H).

(+/-)-Endo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene (XVIII).

A solution of N-(3-pyridylidene)-ethylamine (XVII) (1g, 7.46 mmol) in dry methylene chloride (10 mL, freshly distilled over P_2O_5) was stirred for 30 min. with powdered 4Å molecular sieves (5g) under nitrogen. Titanium chloride (0.82 mL,7.46 mmol) was then added, and the resulting mixture stirred for an additional 30 min. The mixture was cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (1.35 mL, 14.92 mmole) in dry methylene chloride (5 mL). The reaction mixture was allowed to warm to ambient temperature overnight. Chloroform (10 mL) was added to the mixture, and the solution was filtered through a bed of Celite. The filterate was evaporated to dryness and the resulting residue was dissolved by addition of a 10% (w/v) aqueous solution of sodium hydroxide. The resulting solution was stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to give 1.04g of a crude brown syrup which was shown by ^1H NMR to be a mixture of endo-and exo-isomers (ratio 70:30, respectively). The pure (+/-)-endo-isomer R_f=0.62 (solvent system: chloroform-methanol (90:10, v/v)) (700mg, 47%) was obtained by column chromatography of the mixture over silica (200-400 mesh) using 5% of methanol in chloroform as eluent.

^1H NMR ($CDCl_3$) : δ 8.72 (d,1H), 8.78-8.62 (dd, 1H), 7.88-7.82 (m, 1H), 7.28-7.20 (m, 1H), 6.56-6.50 (m, 1H). 6.22-5.96 (m. 1H), 4.01 (d. 1H), 2.78 (s, 1H), 2.70 (s, 1H), 2.6-2.49 (m, 1H), 2.46-2.92 (m, 1H), 1.70-1.64 (d, 1H), 1.62-1.58 (d, 1H), 0.95 (t, 3H).

^{13}C NMR ($CDCl_3$) : δ 149.3, 147.9, 141.3, 137.1, 135.2, 133.4, 123.6, 65.6, 64.5, 51.0, 48.2, 42.2, 14.4.

Sample No. 8 is (+/-)-endo-2-(p-methoxybenzyl)-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

N-(3-pyridylidene)-p-methoxybenzylamine (XX).

The Schiff base (XX) was obtained as described for the preparati n of compound (XVII) using p-methoxybenzylamine (2.56g. 18.69 mmol) in place of ethylamine

and afforded 3.14g (95%) of the desired compound, which was used immediately in the next step without further purification.

^{1}H NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.98 (d, 1H), 8.62 (s, 1H), 8.40 (d, 1H), 7.63-7.50 (m, 2H), 7.22-7.18 (d, 2H), 5.08 (s, 1H), 4.02 (s, 3H).

(+/-)-Endo-2-p-methoxybenzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene (XXI). A solution of N-(3-pyridylidene)-p-methoxybenzylamine (XX) (1.7g, 7.52 mmol) in dry methylene chloride (10 mL, freshly distilled over P_2O_5) was stirred for 30 min. with powdered 3Å molecular sieves (5g) under nitrogen. Titanium chloride (0.82 mL,7.50 mmol) was then added, and the resulting mixture stirred for an additional 30 min. The mixture was cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (1.35 mL, 14.85 mmole) in dry methylene chloride (5 mL). The reaction mixture was allowed to warm to ambient temperature overnight. Chloroform (10 mL) was added to the mixture, and the solution was filtered through a bed of Celite. The filterate was evaporated to dryness and the resulting residue was dissolved by addition of a 10% aqueous solution of sodium hydroxide. The resulting solution was stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to give 1.9g of a crude brown syrup which was shown by ^{1}H NMR to be a mixture of endo-and exo-isomers (ratio 75:25, respectively). The pure (+/-)-endo-isomer R_f=0.60 (solvent system: chloroform-methanol; 95:5 (v/v)) (900mg, 41%) was obtained by silica gel chromatography (200-400 mesh) using 2% of methanol in chloroform as eluent.

^{1}H NMR ($CDCl_3$) : δ 8.75 (d, 1H), 8.44-8.40 (dd, 1H), 7.86-7.80 (m, 1H), 7.26(d, 2H), 7.22-7.16 (m, 1H). 6.80 (d, 2H), 6.62-6.56 (m, 1H), 6.24-6.18 (m, 1H), 3.82 (d, 1H). 3.64 (s. 2H). 3.46 (d. 1H). 3.30 (d. 1H), 2.84 (s, 1H), 2.78 (s, 1H), 1.63 (d, 1H). 1.23 (d. 1H).

^{13}C NMR ($CDCl_3$) : δ 158.2, 149.1. 147.2, 139.1. 137.0. 135.0, 132.2, 131.2, 130, 122.8, 113.2, 64.82, 62.91, 57.18. 55.0, 52.08, 14.2.

Sample No. 9 is (+/-)-endo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

N-(3-pyridylidene)-benzylamine (XXIII).

The procedure described for the preparation of compound (XVII) was used, replacing p-methoxybenzylamine with benzylamine, to obtain 3.26g (98%) of N-(3-pyridylidene)-benzylamine (XXIII).

(+/-)-Endo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene (XXIV).

A solution of N-(3-pyridylidene)-benzylamine (XXIII) (1.0g, 5.1 mmol) in dry methylene chloride (10 mL, freshly distilled over P_2O_5) was stirred for 30 min. with powdered 3Å molecular sieves (5g) under nitrogen. Titanium chloride (0.56 mL, 5.1 mmol) was then added, and the resulting mixture stirred for an additional 30 min. The mixture was cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (0.93 mL, 10.2 mmole) in dry methylene chloride (5 mL). The reaction mixture was allowed to warm to ambient temperature overnight. Chloroform (10 mL) was added to the mixture, and the solution was filtered through a bed of Celite. The filterate was evaporated to dryness and the resulting residue was dissolved by addition of a 10% (w/v) aqueous solution of sodium hydroxide. The resulting solution was stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to give 840mg of a crude brown syrup which was shown by ^{1}H NMR to be a mixture of endo-and exo-isomers (ratio 70:30, respectively). The pure solid (+/-)-endo-isomer R_f=0.52 (solvent system: chloroform-methanol (90:10, v/v) (520mg, 39%) was obtained by silica gel chromatography (200-400 mesh) using 5% of methanol in chloroform as eluent. Mp=49°-50°C.

^{1}H NMR δ 8.72 (s,1H), 8.48-8.42 (dd, 1H), 7.92-7.84 (m, 1H), 7.40-7.20 (m, 6H), 6.65 (t, 1H), 6.80-6.22 (m, 1H), 3.88 (s, 1H), 3.54 (d, 1H), 3.42 (d, 1H), 2.94 (s, 1H), 2.80 (s, 1H), 1.74 (d, 1H), 1.34 (d, 1H).

Sample No. 10 is (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

N-(3-Pyridylidene)methylamine (XXVI).

A mixture of 3-pyridinecarboxaldehyde (2.0 g, 18.6 mmol), methylamine (12 mL, 2.0 M solution in THF) and molecular sieves (3Å, 5.0 g) were stirred for 12 hours under a nitrogen atmosphere. The reaction mixture was then filtered through celite. Concentration of the resulting solution on a rotary evaporator yielded the Schiff base XXVI (2.01 g, 90%) which was used immediately in the next step without further purification.

^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.61 (d, 1H), 8.30 (s, 1H), 7.38-7.24 (m, 1H), 3.56 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 159.5, 151.2, 149.8, 134.2, 131.9, 123.5, 48.3.

(+/-)-Endo-2-methyl-3-(3-Pyridyl)-2-azabicyclo[2.2.1]hept-5-ene (XXVII).

A solution of N-(3-pyridylidene)-methylamine (XXVI) (2.0g, 16.66 mmol) in dry methylene chloride (10 mL, freshly distilled over P_2O_5) was stirred for 30 min. with powdered 3Å molecular sieves (5g) under nitrogen. Titanium chloride (1.82 mL, 16.6 mmol) was then added, and the resulting mixture stirred for an additiona 30 min. The mixture was cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (3.03 mL, 33.33 mmole) in dry methylene chloride (5 mL). The reaction mixture was allowed to warm to ambient temperature overnight. Chloroform (10 mL) was added to the mixture, and the solution was filtered through a bed of Celite. The filterate was evaporated to dryness and the resulting residue was dissolved by addition of a 10% (w/v) aqueous solution of sodium hydroxide. The resulting solution was stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to give 2.5g of a crude brown syrup which was shown by ^{1}H NMR to be a mixture of endo-and exo-isomers (ratio 65:35, respectively). The pure (+/-) endo-isomer R_f=0.51 (solvent system: chloroform-methanol (90:10, v/v) (1.52g, 49%) was obtained by silica gel chromatography (200-400 mesh) using 5% of methanol in chloroform as eluent.

^{1}H NMR ($CDCl_3$): δ 8.69 (d, 1H), 8.49-8.42 (dd, 1H), 7.36-7.28 (m, 1H), 7.26-7.20 (m, 1H), 6.62-6.56 (m, 1H), 6.30-6.19 (dd, 1H), 3.92 (d, 1H), 2.80 (s, 1H), 2.64 (s, 1H), 2.42 (s, 3H), 1.76-1.70 (d, 1H), 1.40-1.34 (d, 1H)

Sample No. 11 is (+/-)-<u>exo</u>-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

<u>(+/-)-Exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene (XXVIII).</u>

The (+/-)-<u>exo</u>-isomer 650 mg (21%) R_f=0.42 (solvent system: methanol-chloroform (10:90, v/v)) was obtained by column chromatography of the isomeric mixture over silica (200-400 mesh) using 5% of methanol in chloroform as eluent. ^{1}H NMR ($CDCl_3$): δ 8.50 (d, 1H), 8.83-8.00 (dd, 1H), 7.62-7.58 (m, 1H), 7.40-7.21 (m, 1H), 6.58-6.50 (m, 1H), 5.60-5.42 (m, 1H), 3.65 (s, 1H), 3.58 (d, 1H), 3.25 (t, 1H), 2.52 (s, 3H), 2.22 (d, 1H), 1.65 (d, 1H).

Sample No. 12 is (+/-)-<u>endo</u>-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene which is prepared essentially in accordance with the following techniques.

<u>Ethyl-5-bromo-3-pyridinecarboxylate (XXXV).</u>

This compound was prepared essentially in accordance with the techniques described by Nutaitis et al, <u>Org. Prep. Proc. Int</u>., Vol. 24, pp. 143-146 (1992) and afforded 9.6g (85%) of compound (XXXV).

<u>5-Bromo-3-pyridinemethylalcohol (XXXVI).</u>

This compound was prepared essentially as described by Nutaitis et al, <u>Org. Prep. Proc. Int</u>., Vol. 24, pp. 143-146 (1992) et al, and afforded 3 g (73%) of compound (XXXVI).

<u>5-Bromo-3-pyridinecarboxaldehyde (XXXVII).</u>

DMSO (2.50 mL, 32 mmol) was added dropwise at -60°C, over a period of 5 min., to a solution of oxalyl chloride (1.45 mL, 16 mmol) in dry methylene chloride (40 mL). The reaction mixture was stirred at -60°C for 2 min., then a solution of 5-bromo-3-pyridinemethylalcohol (3 g, 15.9 mmol) in dry methylene chloride (5 mL) was added over a 15 min. period and the resulting solution was stirred for 15 min. at -60°C. Triethylamine (10mL) was added and the solution was stirred for 5 additional minutes, followed by the addition of water (100mL). The reaction mixture was all wed to warm to room temperature and extracted with chloroform (4x25 mL). The organic extracts were dried over anhydrous

Na_2SO_4, filtered and evaporated on a rotary evaporator to give 3 g of a thick syrup. The pure compound (XXXVII) (2.5g, 84%) was obtained after column chromatography over silica gel (200-400 mesh) using chloroform-methanol (98:2, v/v) as eluent.

^{1}H NMR ($CDCl_3$): δ 10.00 (s, 1H), 8.92 (s, 1H), 8.82 (s, 1H), 8.22 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 189.1, 155.4, 149.0, 138.2, 132.0, 122.3.

N-3-[3-(5-Bromopyridylidene)]methylamine (XXXVIII).

A mixture of 5-bromo-3-pyridinecarboxaldehyde (0.5g, 2.69mmol), methylamine (6mL, 2.0 M solution in THF) and molecular sieves (3Å, 3.0 g) were stirred for 12 hours under a nitrogen atmosphere. The reaction mixture was then filtered through celite. Concentration of the resulting solution on a rotary evaporator yielded the Schiff base XXXVII (508 mg, 95%) which was used immediately in the next step without further purification.

^{1}H NMR ($CDCl_3$): δ 8.78-8.62 (m, 2H), 8.23 (m, 2H), 3.58 (s, 3H).

(+/-)-Endo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene (XXXIX).

A solution of N-[3-(5-bromopyridylidene)methylamine (XXXVIII) (500 mg, 2.51 mmol) in dry methylene chloride (5 mL, freshly distilled over P_2O_5) was stirred for 30 min. with powdered 3Å molecular sieves (3g) under nitrogen. Titanium chloride (0.28 mL, 2.5 mmol) was then added. and the resulting mixture stirred for an additional 30 min. The mixture was cooled to -78°C (dry ice-acetone bath) before addition of a solution of freshly distilled cyclopentadiene (0.45 mL, 5.02 mmol) in dry methylene chloride (3 mL).The reaction mixture was allowed to warm to ambient temperature overnight. Chloroform (10 mL) was added to the mixture, and the solution was filtered through a bed of Celite. The filterate was evaporated to dryness and the resulting residue was dissolved by addition of a 10% aqueous solution of sodium hydroxide. The resulting solution was stirred for 10 min. and extracted with chloroform (4x10 mL). The extracts were dried over anhydrous K_2CO_3, filtered, and evaporated to give 0.6 g of a crude brown syrup which was shown by ^{1}H NMR to be a mixture of endo-and exo-isomers (ratio 65:35, respectively). The pure (+/-)-endo isomer (250 mg. 37%), R_f=0.45 (solvent system: methanol-chloroform (1:6. v/v)) was obtained after column

chromatography over silica gel (200-400 mesh, 60 Å) using acetonitrile in chloroform (1:6, v/v) as eluent.

^{1}H NMR ($CDCl_3$): δ 8.49 (d, 1H), 8.15 (d, 1H), 8.70 (t, 1H), 6.50-6.43 (m, 1H), 6.16-6.11 (m, 1H), 3.81 (s, 1H), 2.70 (s, 1H), 2.54 (s, 1H), 2.14 (s, 3H), 1.61-1.55 (d, 1H), 1.30-1.25 (d, 1H).

For comparison purposes, Sample No. C-1 was provided. This sample is (S)-(-)-nicotine, which has been reported to have demonstrated a positive effect towards the treatment of various CNS disorders.

Determination of binding of compounds to relevant receptor sites

Rats (Sprague-Dawley) were maintained on a 12 hour light/dark cycle and were allowed free access to water and food supplied by Wayne Lab Blox, Madison, WI. Animals used in the present studies weighed 200 to 250 g. Brain membrane preparations were obtained from brain tissue of either males or females.

Rats were killed by decapitation following anesthesia with 70% CO_2. Brains were removed and placed on an ice-cold platform. The cerebellum was removed and the remaining tissue was placed in 10 volumes (weight:volume) of ice-cold buffer (Krebs-Ringers HEPES: NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 2.5 mM; $MgSO_4$, 1.2 mM; HEPES, 20 mM; pH to 7.5 with NaOH) and homogenized with a glass-Teflon tissue grinder. The resulting homogenate was centrifuged at 18,000 x g for 20 min. and the resulting pellet was resuspended in 20 volumes of water. After 60 min. incubation at 4 °C, a new pellet was collected by centrifugation at 18,000 x g for 20 min. After resuspension in 10 volumes of buffer, a new final pellet was again collected by centrifugation at 18,000 x g for 20 min. Prior to each centrifugation step, the suspension was incubated at 37 °C for 5 min. to promote hydrolysis of endogenous acetylcholine. The final pellet was overlayered with buffer and stored at -70 °C. On the day of the assay, that pellet was thawed, resuspended in buffer and centrifuged at 18,000 x g for 20 min. The pellet obtained was resuspended in buffer to a final concentration of approximately 5 mg protein/ml. Protein was determined by the

method of Lowry et al., J. Biol. Chem., Vol. 193, pp. 265-275 (1951), using bovine serum albumin as the standard.

The binding of L-[^{3}H]nicotine was measured using a modification of the method of Romano et al., Science, Vol. 210, pp. 647-650 (1980) as described previously by Marks et al., Mol. Pharmacol., Vol. 30, pp. 427-436 (1986). The L-[^{3}H]nicotine used in all experiments was purified chromatographically by the method of Romm, et al., Life Sci., Vol. 46, pp. 935-943 (1990). The binding of L-[^{3}H]nicotine was measured using a 2 hr. incubation at 4 °C. Incubations contained about 500 ug of protein and were conducted in 12 mm x 75 mm polypropylene test tubes in a final incubation volume of 250 ul. The incubation buffer was Krebs-Ringers HEPES containing 200 mM TRIS buffer, pH 7.5. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (Micro Filtration Systems) that had been soaked in buffer containing 0.5 percent polyethyleneimine. Filtration vacuum was -50 to -100 torr. Each filter was washed five times with 3 ml of ice-cold buffer. The filtration apparatus was cooled to 2 °C before use and was kept cold through the filtration process. Nonspecific binding was determined by inclusion of 10 uM nonradioactive nicotine in the incubations.

The inhibition of L-[^{3}H]nicotine binding by test compounds was determined by including one of eight different concentrations of the test compound in the incubation. Inhibition profiles were measured using 10 nM L-[^{3}H]nicotine and IC_{50} values were estimated as the concentration of compound that inhibited 50 percent of specific L-[^{3}H]nicotine binding. Inhibition constants (Ki values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

Determination of Dopamine Release

Dopamine release was measured by preparing synaptosomes from the striatal area of rat brain obtained from Sprague-Dawley rats generally according to the procedures set forth by Nagy et al., J. Neurochem., Vol. 43, pp. 1114-1123 (1984). Striata from 4 rats were homogenized in 2 ml of 0.32M

sucrose buffered with 5 mM HEPES (pH 7.5), using a glass-Teflon tissue grinder. The homogenate was diluted to 5 ml with additional homogenization solution and centrifuged at 1,000 x g for 10 min. This procedure was repeated on the new pellet and the resulting supernatant was centrifuged at 12,000 x g for 20 min. A 3 layer discontinuous Percoll gradient consisting of 16 percent, 10 percent and 7.5 percent Percoll in HEPES-buffered sucrose was made with the final pellet dispersed in the top layer. After centrifugation at 15,000 x g for 20 min., the synaptosomes were recovered above the 16 percent layer with a Pasteur pipette, diluted with 8 ml of perfusion buffer (128 mM NaCl, 2.4 mM KCl, 3.2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25 mM HEPES pH 7.4, 10 mM dextrose, 1 mM ascorbate, 0.01 mM pargyline), and centrifuged at 15,000 x g for 20 min. The new pellet was collected and re-suspended in perfusion buffer. The synaptosome suspension was incubated for 10 min. at 37 °C. [^{3}H]-Dopamine (Amersham, 40-60 Ci/mmol) was added to the suspension to give a final concentration of 0.1 uM, and the suspension was incubated for another 5 min. Using this method, 30 to 90 percent of the dopamine was taken up into the synaptosomes, as determined by scintillation counting following filtration through glass fiber filters soaked with 0.5 percent polyethyleneimine. A continuous perfusion system was used to monitor release following exposure to each ligand. Synaptosomes were loaded onto glass fiber filters (Gelman type A/E). Perfusion buffer was dripped onto the filters (0.2-0.3 ml/min.) and pulled through the filters with a peristaltic pump. Synaptosomes were washed with perfusion buffer for a minimum of 20 min. before addition of the ligand. After the addition of 0.2 ml of a solution containing various concentrations of ligand, the perfusate was collected into scintillation vials at 1 min. intervals and the dopamine released was quantified by scintillation counting. Peaks of radioactivity released above background were summed and the average basal release during that time was subtracted from the total. Release was expressed as a percentage of release obtained with an equal concentration of (S)-(-)-nicotine.

Determination of Log P

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968)), were calculated according to the methods described by Hopfinger, Conformational Properties of Macromolecules, Academic Press (1973) using Cerius^2 software package by Molecular Simulations, Inc.

Determination of Interaction with Muscle

Human muscle activation was established on the human clonal line TE671/RD which is derived from an embryonal rhabdomyosarcoma (Stratton et al., Carcinogen, Vol. 10, pp. 899-905 (1989)). As evidenced through pharmacological (Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989)), electrophysiological (Oswald et al, Neurosci. Lett., Vol. 96, pp. 207-212 (1989)), and molecular biological studies (Luther et al., J. Neurosci., Vol. 9, pp. 1082-1096 (1989)) these cells express muscle-like nicotinic receptors. Nicotinic acetylcholine receptor (nAChR) function was assayed using $^{86}Rb^+$ efflux according to a method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine.

Determination of Interaction with Ganglia

Ganglionic effects were established on the rat pheochromocytoma clonal line PC12, which is a continuous clonal cell line of neural crest origin derived from a tumor of the rat adrenal medulla expressing ganglionic-type neuronal nicotinic receptors (see Whiting et al., Nature, Vol. 327, pp. 515-518 (1987); Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989); Whiting et al., Mol. Brain Res., Vol. 10, pp. 61-70 (1990)). Discussion concerning the heterogeneity of nicotinic receptors subtypes is set forth in Lukas et al., Internatl. Review Neurobiol., Vol. 34, pp. 25-130 (1992). Acetylcholine nicotinic receptors expressed in rat ganglia share a very high degree of homology with their human counterparts. See, Fornasari et al., Neurosci. Lett., Vol. 111,

pp. 351-356 (1990) and Chini et al., Proc. Natl. Acad. Sci. USA , Vol. 89, pp. 1572-1576 (1992). Both clonal cell lines described above were maintained in proliferative growth phase according to routine protocols (Bencherif et al., Mol. Cell. Neurosci., Vol. 2, pp. 52-65, (1991) and Bencherif et al., J. Pharmacol. Exp. Ther., Vol. 257, pp. 946-953 (1991)). Intact cells on dishes were used for functional studies. Routinely, sample aliquots were reserved for determination of protein concentration using the method of Bradford, Anal. Biochem., Vol. 72, pp. 248-254 (1976) with bovine serum albumin as the standard. Nicotinic acetylcholine receptor (nAChR) function was assayed using $^{86}Rb^{+}$ efflux according to a method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Cells were plated in 35-mm diameter wells of 6-well dishes for at least 48 hours and loaded for at least 4 hours at 37 °C in a medium containing serum, and 1μCi/ml $^{86}Rb^{+}$. Following removal of the loading medium, cells were quickly washed three times with label-free Ringer's solution and exposed for 4 minutes at 20 °C to 900 μl of Ringer's containing the indicated concentration of compound to be tested (to define total efflux) or in addition to 100 μM mecamylamine (to define non-specific efflux). The medium was removed and $^{86}Rb^{+}$ was quantitated using Cerenkov detection (see Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988)). Specific ion efflux was determined as the difference in isotope efflux between total and non-specific efflux samples. The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine. Data are presented in Table I.

Sample Nos. 2, 4 and 11, which have an exo form, exhibit good high affinity binding to CNS nicotinic receptors. In addition, Sample Nos. 5 and 6, which have neither an exo nor endo form, exhibit good high affinity binding to CNS nicotinic receptors. Sample No. 10, which has an endo form, exhibits good high affinity binding to CNS nicotinic receptors. Sample Nos. 8 and 9 induce dopamine release and exhibit desirably low effects at muscle sites and ganglionic sites. Sample Nos. 4, 5, 6 and 10 exhibit good high affinity binding to CNS nicotinic receptors and exhibit desirably low effects at muscle sites and ganglionic sites. The data in Table I indicate that the compounds have the

capability of passing the blood-brain barrier by virtue of their favorable logP values. Certain compounds exhibit binding to high affinity CNS nicotinic receptors as indicated by their low binding constants. Certain compounds induce activation of CNS nicotinic receptors of a subject and cause neurotransmitter release, and thereby have the capability of demonstrating known nicotinic pharmacology. Thus, the data indicate that such compounds have the capability of being useful in treating CNS disorders involving nicotinic cholinergic systems. Furthermore, the data indicate that certain compounds do not cause any appreciable effects at muscle sites and ganglionic sites, thus indicating the potential for a lack of undesirable side effects in subjects receiving administration of those compounds.

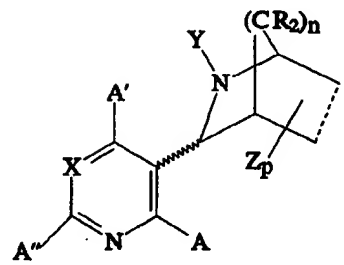
TABLE 1

Sample No.	Ki(nM)	logP	Dopamine Release		Muscle Effect	Ganglion Effect
			EC50 (nM)	Emax (% nicotine)	(% nicotine)	(% nicotine)
C-1*	2	0.71	115	100	100	100
1	476	1.7	550	14	69	12
2	2	1.7	300	41	103	65
3	6359	1.9	13000	9	0	0
4	33	1.9	35000	17	8	8
5	35	1.9	2550	4	9	3
6	58	2.1	2000	10	30	21
7	7815	2.0	12900	22	18	2
8	80767	3.2	>100000	15**	0	0
9	141000	3.1	11000	30	7	11
10	3	1.4	86	44	25	18
11	9	1.5	90	58	7	55
12	2101	1.4	1650	12	2	4

* not an example of the invention
Emax at 100 uM

WHAT IS CLAIMED IS:

1. A compound having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value which is between about -0.3 and about 0.75; n is an integer which ranges from 1 to 2; R individually represents hydrogen or alkyl containing one to five carbon atoms; Z represents alkyl containing one to five carbon atoms; A and A' individually represent hydrogen, alkyl containing one to seven carbon atoms, or halo; A'' represents hydrogen, alkyl containing one to seven carbon atoms, halo or an aromatic group-containing species; the dashed line in the structure represents a C-C single bond or a C-C double bond; the wavy line in the structure represents that the compound can have an <u>endo</u> or <u>exo</u> form; p is an integer ranging from 0 to 7 when the dashed line is a C-C single bond, and an integer ranging from 0 to 5 when the dashed line is a C-C double bond; and Y represents hydrogen, alkyl containing one to seven carbon atoms or an aromatic group-containing species.

2. The compound of Claim 1 wherein p is 0 or 1.

3. The compound of Claim 1 wherein p is 0.

4. The compound of Claim 1 wherein R is hydrogen.

5. The compound of Claim 1 wherein A and A' are hydrogen.

6. The compound of Claim 1 wherein A and A' are hydrogen, and A'' is methyl or ethyl.

7. The compound of Claim 1 wherein A, A' and A'' are hydrogen.

8. The compound of Claim 1 wherein X is a member of the group consisting of N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'', C-CF_3, C-OH, C-CN, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR', C-C(=O)N R'R'', C-NR'C(=O)R', C-C(=O)OR', C-OC(=O)R', C-OC(=O)NR'R'' and C-NR'C(=O)OR', where R' and R'' are individually hydrogen or alkyl containing one to five carbon atoms.

9. The compound of Claim 1 having the form of (+/-)-exo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

10. The compound of Claim 1 having the form of (+/-)-exo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

11. The compound of Claim 1 having the form of (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

12. The compound of Claim 1 having the form of (+/-)-exo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

13. The compound of Claim 1 having the form of (+/-)-exo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

14. The compound of Claim 1 having the form of (+/-)-exo-2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

15. The compound of Claim 1 having the form of (+/-)-exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

16. The compound of Claim 1 having the form of (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

17. The compound of Claim 1 having the form of (+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

18. The compound of Claim 1 having the form of (+/-)-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

19. The compound of Claim 1 wherein the dashed line is a C-C double bond and Y is alkyl containing 1 to 4 carbon atoms.

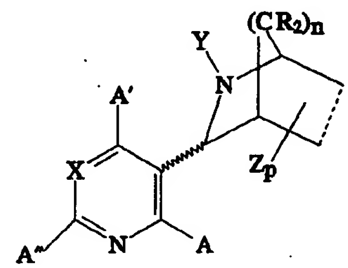
20. A pharmaceutical composition comprising a compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier.

21. A pharmaceutical composition according to claim 20, comprising said compound in an amount effective to treat a central nervous system disorder characterized by a decrease in nicotinic receptor activity.

22. A pharmaceutical composition according to claim 20, comprising said compound in an amount effective to treat a neurodegenerative central nervous system disorder.

23. A pharmaceutical composition according to claim 20, comprising said compound in an amount effective to treat senile dementia of the Alzheimer's type.

24. The use of a compound having the formula:



for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where X is nitrogen or carbon bonded to a substitutent species characterized as having a sigma m value which is between about -0.3 and about 0.75; n is an integer which ranges from 1 to 2; R individually represents hydrogen or alkyl containing one to five carbon atoms; Z represents alkyl containing one to five carbon atoms; A and A' individually represent hydrogen, alkyl containing one to seven carbon atoms, or halo; A'' represents hydrogen, alkyl containing one to seven carbon atoms, halo or an aromatic group-containing species; the dashed line in the structure represents a C-C single bond or a C=C double bond; the wavy line in the structure represents that the compound can have an <u>endo</u> or <u>exo</u> form; p is an integer ranging from 0 to 7 when the dashed line is a C-C single bond, and an integer ranging from 0 to 5 when the dashed line is a C-C double bond; and Y represents hydrogen, alkyl containing one to seven carbon atoms or an aromatic group-containing species.

25. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where p is 0 or 1.

26. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where p is 0.

27. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where R is hydrogen.

28. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where A and A' are hydrogen.

29. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where A and A' are hydrogen, and A''is methyl or ethyl.

30. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where A, A' and A''are hydrogen.

31. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where X is a member of the group consisting of N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'', $C\text{-}CF_3$, C-OH, C-CN, C-SH, $C\text{-}SCH_3$, $C\text{-}N_3$, $C\text{-}SO_2CH_3$, C-OR', C-C(=O)N R'R''C-NR'C(=O)R', C-C(=O)OR', C-OC(=O)R', C-OC(=O)NR'R''and C-NR'C(=O)OR', where R' and R''are individually hydrogen or alkyl containing one to five carbon atoms.

32. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

33. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

34. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

35. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

36. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-benzyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

37. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-para-anisyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

38. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

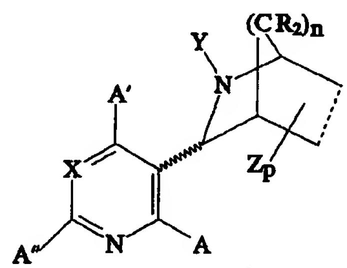
39. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

40. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

41. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, where the compound of Claim 1 has the form of (+/-)-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

42. The use of a compound of Claim 24 for the preparation of a medicament for the prevention or treatment of a central nervous system disorder, wherein the dashed line of the compound is a C-C double bond and Y is alkyl containing 1 to 4 carbon atoms.

43. A method for providing prevention or treatment of a central nervous system disorder, the method comprising administering to a subject an effective amount of a compound having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value which is between about -0.3 and about 0.75; n is an integer which ranges from 1 to 2; R individually represents hydrogen or alkyl containing one to five carbon atoms; Z represents alkyl containing one to five carbon atoms; A and A' individually represent hydrogen, alkyl containing one to seven carbon atoms, or halo; A'' represents hydrogen, alkyl containing one to seven carbon atoms, halo or an aromatic group-containing species; the dashed line in the structure represents a C-C single bond or a C-C double bond; the wavy line in the structure represents that the compound can have an <u>endo</u> or <u>exo</u> form; p is an integer ranging from 0 to 7 when the dashed line is a C-C single bond, and an integer ranging from 0 to 5 when the dashed line is a C-C double bond; and Y represents hydrogen, alkyl containing one to seven carbon atoms or an aromatic group-containing species.

44. The method of Claim 43 whereby p is 0 or 1.

45. The method of Claim 43 whereby p is 0.

46. The method of Claim 43 whereby R is hydrogen.

47. The method of Claim 43 whereby A and A' are hydrogen.

48. The method of Claim 43 whereby A and A' are hydrogen, and A''is methyl or ethyl.

49. The method of Claim 43 whereby A, A' and A''are hydrogen.

50. The method of Claim 43 whereby X is a member of the group consisting of N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'',C-CF_3, C-OH, C-CN, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR', C-C(=O)N R'R'',C-NR'C(=O)R', C-C(=O)OR', C-OC(=O)R', C-OC(=O)NR'R''and C-NR'C(=O)OR', where R' and R''are individually hydrogen or alkyl containing one to five carbon atoms.

51. The method of Claim 43 whereby the compound is (+/-)-exo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(5-bromopyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

52. The method of Claim 43 whereby the compound is (+/-)-exo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-[3-(6-methylpyridyl)]-2-azabicyclo[2.2.1]hept-5-ene.

53. The method of Claim 43 whereby the compound is (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

54. The method of Claim 43 whereby the compound is (+/-)-exo-2-ethyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.1]hept-5-ene.

55. The method of Claim 43 whereby the compound is (+/-)-exo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

56. The method of Claim 43 whereby the compound is (+/-)-exo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene or (+/-)-endo-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene.

57. The method of Claim 43 whereby the compound is (+/-)-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

58. The method of Claim 43 whereby the compound is (+/-)-2-methyl-3-(3-pyridyl)-2-azabicyclo[2.2.2]octane.

59. The method of Claim 43 whereby the compound is such that the dashed line is a C-C double bond and Y is alkyl containing 1 to 4 carbon atoms.

60. The method of Claim 43 wherely the central nervous system disorder is a neurodegenerative disease.

61. The method of Claim 60 whereby the neurodegenerative disease is senile dementia of the Alzheimer's type.

62. The method of Claim 43 whereby the compound is such that the dashed line is a C-C single bond

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 96/04536

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/08 A61K31/465 //(C07D471/08,221:00,221:00),
(C07D471/08,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 03306 (DU PONT ;PIOTROWSKI DAVID WALTER (US)) 2 February 1995 see page 1, formula I, Q-2; pages 22, 23, tables 4, 5	1-8, 10-13, 15-19
Y	EP,A,0 412 798 (MERCK SHARP & DOHME) 13 February 1991 see the whole document	1-62
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A	WO,A,95 07078 (CYTOMED INC ;UNIV VIRGINIA (US); QIAN CHANGGENG (US); LI TONGCHUAN) 16 March 1995 see claims	1-62

☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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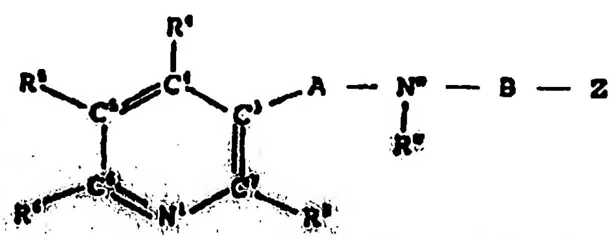
(54) Title: SUBSTITUTED PYRIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS MODULATORS OF ACETYLCHOLINE RECEPTORS

(57) Abstract

In accordance with the present invention, there are provided compounds having the structure (I), wherein: A, B, N^a, R^a, Z, R^2, R^4, R^5 and R^6 are defined as in the description. The compounds of the invention displace acetylcholine receptor ligands from their binding sites. Invention compounds may act as agonists, partial agonists, antagonists or allosteric modulators of acetylcholine receptors, and are useful for a variety of therapeutic applications, such as the treatment of Alzheimer's disease and other disorders involving memory loss and/or dementia (including AIDS dementia); disorders of attention and focus (such as attention deficit disorders); disorders of extrapyramidal motor function such as Parkinson's disease, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia; mood and emotional disorders such as depression, panic, anxiety and psychosis; substance abuse including withdrawal syndromes and substitution therapy; neuroendocrine disorders and dysregulation of food intake, including bulimia and anorexia; disorders of nociception and control of pain; autonomic disorders including dysfunction of gastrointestinal motility and function such as inflammatory bowel disease, irritable bowels syndrome, diarrhea, constipation, gastric acid secretion and ulcers; pheochromocytoma, cardiovascular dysfunction including hypertension and cardia arrhythmias, comedication in surgical procedures, and the like.



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SUBSTITUTED PYRIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS MODULATORS OF ACETYLCHOLINE RECEPTORS

The present invention relates to novel compounds which are capable of modulating acetylcholine receptors. Invention compounds are useful, for example, for treatment of dysfunction of the central or autonomic nervous systems including dementia, cognitive disorders, neurodegenerative disorders, extrapyramidal disorders, convulsive disorders, cardiovascular disorders, endocrine disorders, pain, gastrointestinal disorders, eating disorders, affective disorders, and drug abuse. In addition, the present invention relates to pharmaceutical compositions containing these compounds, as well as various uses therefor.

BACKGROUND OF THE INVENTION

By modulation of neurotransmitter release (including dopamine, norepinephrine, acetylcholine and serotonin) from different brain regions, acetylcholine receptors are involved in the modulation of neuroendocrine function, respiration, mood, motor control and function, focus and attention, concentration, memory and cognition, and the mechanisms of substance abuse. Ligands for acetylcholine receptors have been demonstrated to have effects on attention, cognition, appetite, substance abuse, memory, extrapyramidal function, cardiovascular function, pain and gastrointestinal motility and function. The distribution of acetylcholine receptors that bind nicotine, i.e., nicotinic acetylcholine receptors, is widespread in the brain, including the basal ganglia, limbic system, cerebral cortex and mid- and hind-brain nuclei. In the periphery, the distribution includes muscle, autonomic ganglia, th gastrointestinal tract and the cardiovascular system.

Acetylcholine receptors have been shown to be decreased, *inter alia*, in the brains of pati nts suffering

from Alzheimer's disease or Parkinson's disease, diseases associated with dementia, motor dysfunction and cognitive impairment. Such correlations between acetylcholine receptors and nervous system disorders suggest that compounds that modulate acetylcholine receptors will have beneficial therapeutic effects for many human nervous system disorders. Thus, there is a continuing need for compounds which can selectively modulate the activity of acetylcholine receptors. In response to such need, the present invention provides a new family of compounds which modulate acetylcholine receptors.

BRIEF DESCRIPTION OF THE INVENTION

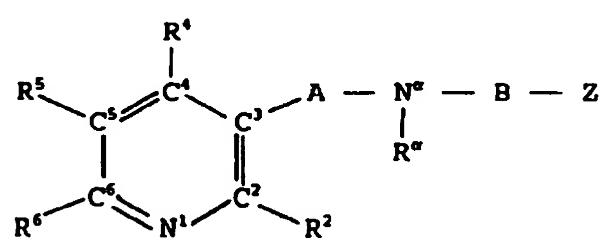
In accordance with the present invention, we have discovered that the class of pyridine compounds defined herein are modulators of acetylcholine receptors.

The compounds of the present invention are capable of displacing one or more acetylcholine receptor ligands, e.g., ^{3}H-nicotine, from mammalian cerebral membrane binding sites. Invention compounds may act as agonists, partial agonists, antagonists or allosteric modulators of acetylcholine receptors. Therapeutic indications for compounds with activity at acetylcholine receptors include diseases of the central nervous system such as Alzheimer's disease and other disorders involving memory loss and/or dementia (including AIDS dementia); cognitive dysfunction (including disorders of attention, focus and concentration), disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia; mood and emotional disorders such as depression, panic, anxiety and psychosis; substance abuse including withdrawal syndromes and substitution therapy; neuroend crin disorders and dysr gulation f food intak , including bulemia and an r xia; disord rs of

nociception and control of pain; autonomic disorders including dysfunction of gastrointestinal motility and function such as inflammatory bowel disease, irritable bowel syndrome, diarrhea, constipation, gastric acid secretion and ulcers; pheochromocytoma; cardiovascular dysfunction including hypertension and cardia arrhythmias, as well as co-medication uses in surgical applications.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds having the structure (Formula I):



I

wherein:

A is a 1, 2, 3, 4, 5 or 6 atom bridging species linking C^3 of the pyridine ring with N^{α}, wherein A is selected from a straight chain or branched chain alkylene moiety having up to six atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to six atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to six atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, -S-, -S(O)- and/or -S(O)$_2$-containing alkyl n moiety; provided, however, that any h teroatom contained in A is separated from N^{α} by at least three carbon atoms; and further provided that when

A is a -C(O)- or -C(S)- containing alkylen moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety of A and N^{α}; and further provided that N^{α} is not conjugated with an alkenyl or alkynyl moiety,

wherein A and B can optionally combine to form a monocyclic ring containing A, N^{α} and B, wherein at least one methylene unit intervenes between such ring and C^3 of the pyridine ring;

B is a 1, 2, 3 or 4 atom bridging species linking N^{α} with Z,

wherein B is selected from a straight chain or branched chain alkylene moiety having up to four atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to four atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to four atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, $-N^{\beta}(R^{\beta})-$, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moiety, wherein R^{β} is hydrogen or a lower alkyl moiety; provided, however, that any heteroatom contained in B is separated from N^{α} by at least 2 carbon atoms, and further provided that when B is a -C(O)- or -C(S)- containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety and N^{α}; and further provid d that N^{α} is not conjugat d with an alkenyl or alkynyl moiety, and

wherein B and R^a can optionally combin to form a monocyclic ring containing B, R^a and N^a;

Z is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl, or $-OR^Z$, wherein R^Z is hydrogen, lower alkyl or aryl, or

Z is not present when A and B cooperate to form a ring containing A, N^a and B, or when R^a and B cooperate to form a ring containing B, R^a and N^a;

R^a is selected from hydrogen or lower alkyl; and

R^2, R^4, R^5 and R^6 are each independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$, $-S(O)_2OR'$ or $-S(O)_2NHR'$, wherein each R' is independently hydrog n, lower alkyl, alk nyl, alkynyl or aryl; provided, h wev r, that when R^2, R^4, R^5 or R^6 is $-S(O)R'$, R' is not hydrogen; and

furth r provid d that when R' is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom;

-C(O)R", wherein R" is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

-OR''' or -NR'''$_2$, wherein each R''' is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the -OR''' or -NR'''$_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substitut d alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl,

substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

-SiR'''''$_3$, wherein R''''' is selected from alkyl or aryl.

Specifically excluded from the above definition of compounds embraced by Formula I are compounds wherein A is $-CH=CH-(CH_2)_{1-5}-CH_2-$, B is alkyl, Z is H or absent, R^a is H, and each of R^2, R^4, R^5 and R^6 are independently alkyl or halo; compounds wherein A is $-(CH_2)_{1-5}-$, B and R^a combine to form a B, R^a, N^a ring such that B and R^a together are C_4R_8 or C_5R_{10}, wherein R is hydrogen or alkyl, and Z is absent; compounds wherein A is $-C(O)-(CH_2)_{1-5}-$, B is alkyl, Z is absent or H, R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are alkyl or halo; compounds wherein A is $-CH_2-$, B is $-CH_2-$ or $-CH_2-CH_2-$, Z is H, R^a is $-CH_3$ or $-CH_2-CH_3$, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-$, B is $-CH_2-CH(CH_3)-CH_2-R$, wherein R is *para-tertiary*butylphenyl, Z is absent, R^a is CH_3 or butyl, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-(CHR)_n$, wherein R is H or alkyl and n = 0 or 1, B is $-(CH_2)_n-CHR-CH(X)-$, wherein R is H, methyl or ethyl, X is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), and n = 0 or 1, Z is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are selected from hydrogen, alkyl or alkenyl; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-$, $-CH_2-C_6H_4-$ or $-CH_2-C_{10}H_6-$, Z is hydrogen, $-C_6H_5$, or $-C_{10}H_7$, R^a is CH_3, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-(CH_2)-$, Z is hydrogen, R^a is hydrogen, and ach of R^2, R^4, R^5 and R^6 are hydrog n; comp unds wherein A is $-CH(CH_3)-$, B is $-CH_2-CH_2-[2,3-(OR)_2C_6H_3]$, wher in R is methyl or benzyl,

and R^{α} is hydrog n, or B and R^{α} combine to form a B, R^{α}, N^{α} ring such that B and R^{α} together are $-C(=CH_2)-[1,2-(3,4(OR)_2benzo]-CH_2CH_2-$, wherein R is methyl or benzyl, Z in all instances is absent, and each of R^2, R^4, R^5 and R^6 are hydrogen; as well as compounds wherein A is $-CH(CH_3)-$ or $-CH_2-CH_2-CH_2-$, B is $-CH_2-CH_2-CH(C_6H_5)-$ or $-CH(CH_3)-C_6H_5$, Z is phenyl or absent, R^{α} is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen.

As employed herein, "lower alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 4 carbon atoms; "alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 12 carbon atoms; "substituted alkyl" refers to alkyl radicals further bearing one or more substituents such as hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), aryl, heterocyclic, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl, sulfonamide, and the like;

"cycloalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituents as set forth above;

"alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently being preferred), and "substituted alkenyl" refers to alkenyl radicals further bearing on or more substituents as s t forth above;

"alkynyl" ref rs to straight r branched chain hydr carbyl radicals having at l ast one carbon-carb n

triple bond, and having in the rang of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently being preferred), and "substituted alkynyl" refers to alkynyl radicals further bearing one or more substituents as set forth above;

"aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl radicals further bearing one or more substituents as set forth above;

"alkylaryl" refers to alkyl-substituted aryl radicals and "substituted alkylaryl" refers to alkylaryl radicals further bearing one or more substituents as set forth above;

"arylalkyl" refers to aryl-substituted alkyl radicals and "substituted arylalkyl" refers to arylalkyl radicals further bearing one or more substituents as set forth above;

"arylalkenyl" refers to aryl-substituted alkenyl radicals and "substituted arylalkenyl" refers to arylalkenyl radicals further bearing one or more substituents as set forth above;

"arylalkynyl" refers to aryl-substituted alkynyl radicals and "substituted arylalkynyl" refers to arylalkynyl radicals further bearing one or more substituents as set forth above;

"aroyl" refers to aryl-carbonyl species such as benzoyl and "substituted aroyl" refers to aroyl radicals further bearing on or more substitu nts as set forth above;

"heterocyclic" refers to cyclic (i.e., ring-containing) radicals containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic radicals further bearing one or more substituents as set forth above;

"acyl" refers to alkyl-carbonyl species; and

"halogen" refers to fluoride, chloride, bromide or iodide radicals.

In accordance with the present invention, A is a 1, 2, 3, 4, 5 or 6 atom bridging species which links C^3 of the pyridine ring with N^α of the pyridine side chain. A can be selected from straight chain or branched chain alkylene moieties having up to six atoms in the backbone thereof, or substituted alkylene moieties, straight chain or branched chain alkenylene moieties having up to six atoms in the backbone thereof, or substituted alkenylene moieties, alkynylene moieties having up to six atoms in the backbone thereof, or substituted alkynylene moieties, -O-, -C(O)-, -C(S)-, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moieties; provided, however, that any heteroatom contained in A is separated from N^α by at least three carbon atoms; and further provided that when A is a -C(O)- or -C(S)-containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety of A and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety. Optionally, A and B can combine to form a monocyclic ring containing A, N^α and B, wherein at least one methylene unit intervenes between such ring and C^3 of th pyridin ring. Thus, A can be selected, for exampl , from:

$-CR^A_2-$, wherein each R^A is ind pendently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl;

-(cycloalkyl)-,

$-C(=CXY)-CH_2-$, wherein X and Y are each independently selected from hydrogen, lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, halogen, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, aryloxyalkyl, or $-OR^{AA}$, wherein R^{AA} is lower alkyl or aryl,

and the like.

Preferably, when A is $-C(=CXY)-CH_2-$, X and Y are not both $-OR^{AA}$. Presently preferred compounds are those wherein A is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, -(spirocyclopropyl)-, $-CH=CH-CH_2-CH_2-$, and the like. Especially preferred compounds of the invention are those wherein A is selected from $-CH_2-$ or $-CH(CH_3)-$.

Further in accordance with the present invention, B is a 1, 2, 3 or 4 atom bridging species which links N^α of the pyridine side chain with the terminal group of the side chain, Z. B can be selected from straight chain or branched chain alkylene moieties having up to four atoms in the backbone thereof, or substituted alkylene moieties, straight chain or branched chain alkenylene moieties having up to four atoms in the backbone thereof, or substituted alkenylene moieties, alkynylene moieties having up to four atoms in the backbone thereof, or substituted alkynylene moieties, -O-, -C(O)-, -C(S)-, $-N^\beta(R^\beta)-$, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moi ties, wh rein R^β is hydrogen r a lower alkyl moiety; provided, however, that any heteroatom contain d in B is separat d from N^α by at 1 ast 2 carbon atoms, and further provid d that wh n B is a

$-C(O)-$ or $-C(S)-$ containing alkylene moiety, at least one methylene unit intervenes between the $-C(O)-$ or $-C(S)-$ moiety and N^{α}; and further provided that N^{α} is not conjugated with an alkenyl or alkynyl moiety. Optionally, B and A can combine to form a monocyclic ring containing A, N^{α} and B, wherein at least one methylene unit intervenes between such ring and the pyridine ring. As yet another option, B and R^{α} can combine to form a monocyclic ring containing B, R^{α} and N^{α}. Thus, B can be selected, for example, from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, -(spirocycloalkyl)-, $-CH_2-CH=C(X)-$ (wherein X is as defined above), $-CH_2-C\equiv C-$, $-CH_2CH_2-C(O)-$, and the like. Presently preferred compounds of the invention are those wherein B is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, -(spirocyclopropyl)-, $-CH_2-CH=C(X)-$ (wherein X is H or lower alkyl), $-CH_2-C\equiv C-$ or $-CH_2CH_2-C(O)-$, with $-CH_2-$ presently most preferred.

In accordance with one embodiment of the present invention, A and B can combine to form a ring containing A, N^{α} and B, wherein at least one methylene unit intervenes between such ring and the pyridine ring. Examples of such bridging groups include $-O-CH_2\underset{|}{C}H(CH_2)_n-$, wherein n falls in the range of 1 up to 5, wherein n being 3 or 4 is presently preferred.

As yet another alternative embodiment of the present invention, B and R^{α} can combine to form a ring containing B, R^{α} and N^{α}. Examples of such combination include $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, and the like.

In accordance with the present invention, Z is s lected from hydrogen, alkyl, substituted alkyl, cycloalkyl, ubstituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alk nyl, alkynyl, substitut d alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalk nyl, substituted

arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl, or $-OR^z$, wherein R^z is hydrogen, lower alkyl or aryl. Z is not present, however, when A and B cooperate to form a ring containing A, N^α and B, or when R^α and B cooperate to form a ring containing B, R^α and N^α.

In accordance with the present invention, R^α is selected from hydrogen or lower alkyl.

In accordance with the present invention, R^2, R^4, R^5 and R^6 are each independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$, $-S(O)_2OR'$ or $-S(O)_2NHR'$, wherein each R' is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl; provided, however, that when R^2, R^4, R^5 or R^6 is $-S(O)R'$, R' is not hydrogen; and further provided that when R' is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom;

$-C(O)R''$, wherein R'' is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic,

substituted het rocyclic or trifluorom thyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

-OR''' or -NR'''$_2$, wherein each R''' is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the -OR''' or -NR'''$_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

-SiR'''''$_3$, wherein R''''' is selected from alkyl or aryl.

In accordanc with a preferr d aspect of the pres nt invention, R^5 is alkynyl r substitut d alkynyl having the structure:

$$- C \equiv C - R^{5'}$$

wherein $R^{5'}$ is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$ or $-S(O)_2NHR'$, wherein each R' is as defined above, provided, however, that when R^2, R^4 or R^6 is $-S(O)R'$, R' is not hydrogen, alkenyl or alkynyl, and provided that when R^2, R^4 or R^6 is $-S(O)_2NHR'$, R' is not alkenyl or alkynyl;

$-C(O)R''$, wherein R'' is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

$-OR'''$, wherein R''' is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the $-OR'''$ functionality is not conjugated with an alk nyl or alkynyl functionality;

$-NR'''_2$, wherein each R''' is indep nd ntly as defin d above, r each R''' and the N t which they ar attached can cooperate to form a 4-, 5-,

6- or 7-membered ring; provided, however, that the $-NR'''_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

$-SiR'''''_3$, wherein R''''' is selected from alkyl or aryl, and the like.

In addition, $R^{5'}$ can also be alkylene, substituted alkylene, arylene, substituted arylene, and the like, so that the resulting compound is a polyfunctional species, bearing two or more of the substituted pyridyl structures contemplated by structure I. Thus, R^5 serves as a bridge or linking moiety to couple two or more of the substituted pyridyl structures contemplated by structure I in a single compound.

Presently preferred $R^{5'}$ groups include hydrogen, methyl, ethyl, propyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxymethyl, 2-hydroxy-2-isopropyl, dimethylaminomethyl, phenyl, substituted phenyl (e.g., 3-hydroxyphenyl, 3-hydroxy-4-substituted phenyl (wherein the substitution is methyl, chloro or fluoro)), 4-hydroxyphenyl, 3-substituted-4-hydroxyphenyl (wherein the substitution is methyl, chloro or fluoro), amides ($-CH_2-NH-C(O)-R$, wherein R is selected from hydrogen or lower alkyl), sulfonamid s ($-CH_2-NH-SO_2-R$, wherein R is as defin d abov), and the like.

In accordanc with another preferred asp ct of the present invention, R^5 is an optionally substituted 3- or 4-hydroxyphenyl species. Thus, 3-hydroxyphenyl moieties, as well as 3-hydroxy-4-substituted phenyl moieties are preferred herein, wherein the optional substitution is methyl, chloro or fluoro. In addition, 4-hydroxyphenyl moieties, as well as 3-substituted-4-hydroxyphenyl moieties are also preferred herein, wherein the optional substitution is methyl, chloro or fluoro.

Presently preferred compounds of the invention are those wherein R^2 is hydrogen; wherein R^4 is hydrogen, aryl, alkoxy or aryloxy; wherein R^5 is selected from alkynyl (with ethynyl being especially preferred), aryl, substituted aryl (wherein substituents on the aryl ring are independently selected from one or more of bromine, chlorine, fluorine, phenyl, methoxy, hydroxy, mercaptomethyl and trifluoromethyl substituents being especially preferred), trialkylsilyl, arylalkyl, arylalkenyl or arylalkynyl; wherein R^6 is selected from hydrogen, chlorine, amino, alkyl or alkoxy (with hydrogen, methyl or methoxy being especially preferred); and wherein R^a is hydrogen or methyl.

Particularly preferred compounds of the invention include the compound wherein A = $-CH_2-$ or $-CH_2CH_2-$, B and R^a combined = $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$, Z is not present (due to the linkage of B with R^a), R^2, R^4 and R^6 = H, and R^5 is selected from hydrogen, phenyl, parahydroxyphenyl, 3-chloro-4-hydroxyphenyl, or ethynyl; as well as compounds wherein A is selected from $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or -(spirocyclopropyl)-, B = $-CH_2-$, Z = hydrogen, R^a = H or methyl and R^2, R^4, R^5 and R^6 = H; as well as compounds wherein A = $-C(=CXY)CH_2-$ (wherein X and Y ar ach independently selected from hydrogen, lower alkyl, hydroxyalkyl, fluoro or aryl), B and R^a combined = $-CH_2CH_2CH_2CH_2-$, Z = not pres nt, and R^2, R^4, R^5 and R^6 =

hydrog n. Additional preferred compounds of the invention include those wherein A = $-CH_2-$, B = $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2-C(O)-$, Z = phenyl, substituted phenyl, furanyl or substituted furanyl, imidazolyl, or 3,4-benzopyrrolidine, R^α = hydrogen or methyl, and R^2, R^4, R^5, and R^6 = hydrogen; as well as compounds wherein A and B combined = $-O-CH_2CHCH_2CH_2CH_2-$, thereby forming a ring including A, N^α and B, Z = not present, R^α = methyl, and R^2, R^4, R^5, and R^6 are independently selected from the group set forth above, with the proviso that R^2, R^4, R^5, and R^6 are not hydrogen, alkyl, alkoxy or halogen.

Still further preferred compounds contemplated for use in the practice of the invention include those wherein A = $-CH_2-$ or $-CH_2CH(CH_3)-$, B = $-CH_2-C{\equiv}C-$, Z = hydrogen, R^α = methyl, and R^2, R^4, R^5, and R^6 = hydrogen; as well as those wherein A = $-CH_2-$, B = $-CH_2-CH{=}C(X)-$, wherein X is selected from hydrogen, lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, 778halogen (especially fluoro), aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, aryloxyalkyl, or $-OR^X$, wherein R^X is lower alkyl or aryl, Z = lower alkyl, hydroxyalkyl, trifluoromethyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide, aryl, aryloxyalkyl, or $-OR^Z$, wherein R^Z is lower alkyl or aryl, R^α = methyl, and R^2, R^4, R^5, and R^6 = hydrogen. It is preferred that when X is $-OR^X$, Z is not $-OR^Z$.

Still further preferred compounds of the invention include those wherein A = $-CH_2-$, B = $-CH_2CH_2-C(O)-$ or $-CH_2CH_2-C(O)-NH-$, Z = phenyl or substituted phenyl, R^α = methyl, and R^2, R^4, R^5, and R^6 = hydrogen; as w ll as ompound wherein A = $-CH_2-$ or $-CH(CH_3)-$, B = $-CH_2-$, $-CH(CH_3)-$, or -(cyclopropyl)-, Z = hydrog n, R^α = hydr g n r methyl, and R^2, R^4, R^5, and R^6 = hydrogen.

Additional preferred compounds of th inv nti n include those wherein A = $-CH{=}CH-CH_2-CH_2-$, B = $-CH_2-$, Z = hydrogen, R^a = hydrogen, $R^5 = -C \equiv C - R^{5'}$, wherein $R^{5'}$ is as defined above (with hydrogen, methyl, ethyl, propyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxymethyl, 2-hydroxy-2-isopropyl, dimethylaminomethyl, phenyl, substituted phenyl (e.g., 3-hydroxyphenyl, 3-hydroxy-4-substituted phenyl (wherein the substitution is methyl, chloro or fluoro), 4-hydroxyphenyl, 3-substituted-4-hydroxyphenyl (wherein the substitution is methyl, chloro or fluoro), amides ($-CH_2-NH-C(O)-R$, wherein R is selected from hydrogen or lower alkyl) and sulfonamides ($-CH_2-NH-SO_2-R$, wherein R is as defined above) preferred) or R^5 = 3-hydroxyphenyl, 3-hydroxy-4-substituted phenyl (wherein the optional substitution is methyl, chloro or fluoro), 4-hydroxyphenyl, or 3-substituted-4-hydroxyphenyl (wherein the optional substitution is methyl, chloro or fluoro), and R^2, R^4, and R^6 = hydrogen; as well as compounds wherein A and B combined = $-O-CH_2\underset{|}{C}H(CH_2)_n-$, wherein n is 3 or 4, Z = hydrogen, R^a = hydrogen, $R^5 = -C \equiv C - R^{5'}$, wherein $R^{5'}$ is as defined above (with hydrogen, methyl, ethyl, propyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxymethyl, 2-hydroxy-2-isopropyl, dimethylaminomethyl, phenyl, substituted phenyl (e.g., 3-hydroxyphenyl, 3-hydroxy-4-substituted phenyl (wherein the substitution is methyl, chloro or fluoro), 4-hydroxyphenyl, 3-substituted-4-hydroxyphenyl (wherein the substitution is methyl, chloro or fluoro), amides ($-CH_2-NH-C(O)-R$, wherein R is selected from hydrogen or lower alkyl) and sulfonamides ($-CH_2-NH-SO_2-R$, wherein R is as defined above) preferred) or R^5 = 3-hydroxyphenyl, 3-hydroxy-4-substituted phenyl (wherein the optional substitution is methyl, chloro or fluoro), 4-hydroxyphenyl, or 3-substituted-4-hydroxyph nyl (wherein th opti nal substitution is methyl, chl r r fluoro), and R^2, R^4, and R^6 = hydrog n.

Inventi n compounds have affinity for acetylcholine receptors. As employed herein, the term "acetylcholine receptor" refers to both nicotinic and muscarinic acetylcholine receptors. Affinity of invention compounds for such receptors can be demonstrated in a variety of ways, e.g., via competitive radioligand binding experiments in which the test compounds displace isotopically labelled ligands (such as nicotine, cytisine, methylcarbamylcholine, quinuclidinyl benzilate, and the like) from binding sites in mammalian cerebral membranes. Furthermore, the binding of compounds to acetylcholine receptors can be evaluated as a functional response. For example, the activity of invention compounds can be evaluated employing functional assays based on recombinant neuronal acetylcholine receptor expression systems (see, for example, Williams et al., *Drug News & Perspectives* 7:205-223 (1994)). Test compounds can also be evaluated for their ability to modulate the release of neurotransmitters (e.g., dopamine, norepinephrine, and the like) from rat brain slices (e.g., striatum, hippocampus, and the like). See Examples 14 and 15 for further detail on such techniques. Moreover, test compounds can also be evaluated by way of behavioral studies employing animal models of various CNS, autonomic and cardiovascular disorders (see, for example, D'Amour and Smith, *J. Pharmacol. Exp. Ther.* 72:74-79 (1941) and Iwamoto, *J. Pharmacol. Exp. Ther.* 251:412-421 (1989) for animal models of pain; Klockgether and Turski, *Ann. Neurol.* 28:539-546 (1990), Colpaert, F., *Neuropharmacology* 26:1431-1440 (1987), Ungerstedt and Arbuthknott, *Brain Res.* 24:485-493 (1970), Von Voigtlander and Moore, *Neuropharmacology* 12:451-462 (1973), Ungerstedt et al., *Adv. Neurol.* 3:257-279 (1973), Albanese et al., *N uroscience* 55:823-832 (1993), Janson t al., *Clin. Investig.* 70:232-238 (1992), Sundstrom et al., *Brain Res.* 528:181-188 (1990), Sersh n et al., *Pharmacol. Biochem. Behav.* 28:299-303 (1987) for

animal models of Parkinson's disease; Williams et al., *Gastroenterology* 94:611-621 (1988), Miyata et al., *J. Pharmacol. Exp. Ther.* 261:297-303 (1992), Yamada et al., *Jpn. J. Pharmacol.* 58 (Suppl.):131 (1992) for animal models of irritable bowel syndrome; Coyle et al., *Neurobehav. Toxicol. Tetatol.* 5:617-624 (1983), Schartz et al., *Science* 219:316-318 (1983) for animal models of Huntington's disease; Clow et al., *Euro. J. Pharmacol.* 57:365-375 (1979), Christensen et al., *Psychoparmacol.* 48:1-6 (1976), Rupniak et al., *Psychopharmacol.* 79:226-230 (1983), Waddington et al., *Science* 220:530-532 (1983) for animal models of tardive dyskinesia; Emerich et al., *Pharmacol. Biochem. Behav.* 38:875-880 (1991) for animal models of Gilles de la Tourette's syndrome; Brioni et al., *Eur. J. Pharmacol.* 238:1-8 (1993), Pellow et al., *J. Neurosci. Meth.* 14:149 (1985) for animal models of anxiety; and Estrella et al., *Br. J. Pharmacol* 93:759-768 (1988) for the rat phrenic nerve model which indicates whether a compound has muscle effects that may be useful in treating neuromuscular disorders).

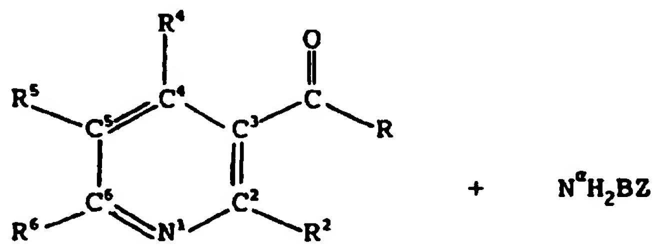
Those of skill in the art recognize that invention compounds may contain one or more chiral centers, and thus can exist as racemic mixtures. For many applications, it is preferred to carry out stereoselective syntheses and/or to subject the reaction product to appropriate purification steps so as to produce substantially optically pure materials. Suitable stereoselective synthetic procedures for producing optically pure materials are well known in the art, as are procedures for purifying racemic mixtures into optically pure fractions.

In accordance with still another mbodiment of the present invention, there are provided methods for the preparation of pyridine compounds as described abov . For

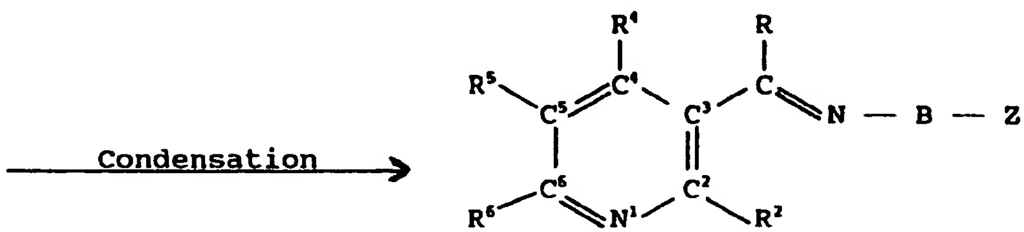
example, many of the pyridine compounds described above can be prepared using synthetic chemistry techniques well known in the art from the acyl pyridine precursor of Formula II as outlined in Scheme I.

Scheme I

Step A

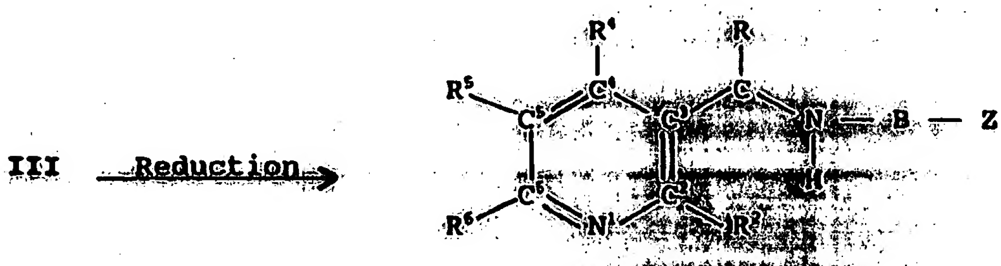


II



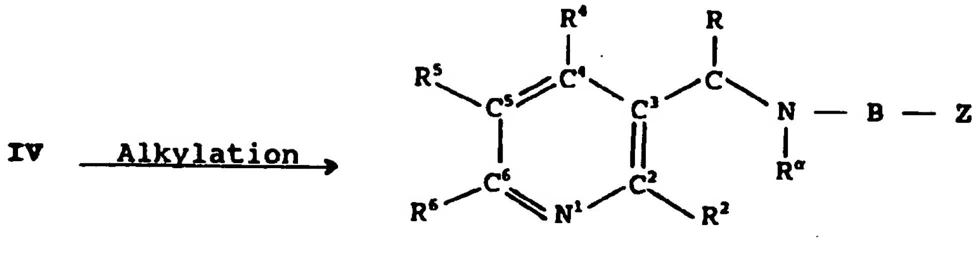
III

Step B



IV

Step C



V

In the above scheme, R^2, R^4, R^5, R^6, R^a, B and Z are as defined above, and R is selected from hydrogen, alkyl, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), aryl, heterocyclic, trifluoromethyl, cyano, carboxyl, carbamate, sulfonyl, sulfonamide, and the like.

In step A of Scheme I, formyl or acyl pyridine of Formula II is coupled with an amine having the general formula N^aH_2BZ to produce an imine of Formula III. This coupling reaction is promoted by a suitable catalyst, such as, for example, titanium tetrachloride, paratoluenesulfonic acid, and the like. The presently preferred catalyst for use in the practice of the present invention is titanium tetrachloride.

The above-described coupling reaction is typically carried out in aprotic solvent, such as, for example, tetrahydrofuran (THF), diethyl ether, tert-butyl methyl ether, 1,2-dimethoxyethane, toluene, and the like. Presently preferred solvents for use in the practice of the present invention are THF and 1,2-dimethoxyethane. The coupling reaction can be carried out over a wid rang of temperatures. Typically reaction temperatures fall in th range of about -78°C up to reflux. Temperatures in th range f about -78°C up to ambi nt ar presently preferred.

R action times requir d to effect the desired coupling reaction can vary widely, typically falling in the range of about 15 minutes up to about 24 hours. Preferred reaction times fall in the range of about 4 up to 12 hours. It is not necessary to purify the product of the above-described coupling reaction (i.e., compound of Formula III), and the resulting reaction product is typically subjected directly to the reduction step described below as step B.

In Step B of Scheme I, imine of Formula III is reduced to produce the secondary amine IV. The desired reduction is typically effected by contacting imine with a suitable hydride source (e.g., sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, sodium triacetoxyborohydride, lithium tri-*tert*-butoxy aluminum hydride, sodium trimethoxy- borohydride, diisobutylaluminum hydride, formic acid, and the like) or by contacting the imine with hydrogen in the presence of a transition metal catalyst (such as, for example, palladium on carbon, Raney Nickel, platinum oxide, tris(triphenylphosphine)rhodium (I) chloride (i.e., Wilkinson's catalyst), palladium hydroxide, and the like). Presently preferred reducing conditions comprise treating imine III with sodium borohydride in a solvent mixture such as methanol/acetic acid, or sodium cyanoborohydride in a suitable solvent system, at a reaction temperature in the range of about -60°C up to about ambient temperature, for in the range of about 1 up to 24 hours. As recognized by those of skill in the art, the selection of reducing agent, reaction time, reaction temperature and reaction media will depend on the specific compound having the Formula III which is being treated.

Alternatively, amines of formula IV can be prepared from II in one st p by contacting th f rmyl r acyl pyridine with an amine in the presence of sodium cyanoborohydride and a catalytic amount of acid (e.g.,

glacial acetic acid) in a suitabl solvent (such as acetonitrile).

Secondary amines of Formula IV can then be recovered from the reaction media by basification, followed by extraction, filtration, and the like. Purification can be achieved by a variety of techniques, such as, for example, chromatography, recrystallization, distillation, and the like. If desired, secondary amines IV can be further converted into acid addition salts.

Since secondary amine IV may have a center of asymmetry, reagents for the above-described reduction reaction can be chosen so as to promote selective reduction to produce amine IV which is substantially enriched in one of the possible enantiomers. In some instances, by judicious choice of reducing agents, each of the possible enantiomers can be prepared in high optical purity. For example, chiral borohydride reducing agents can be employed, as described, for example, by Yamada et al. in *J. Chem. Soc., Perk. 1* 265 (1983), Kawate et al., in *Tetrahedron Asym.* 3, 227 (1992), Mathre et al., *J. Org. Chem.* 58:2880 (1993), or Cho and Chun in *J. Chem. Soc. Perk. 1* 3200 (1990). Alternatively, catalytic hydrogenation in the presence of chiral catalyst can be employed, as described, for example, by Kitamura et al., in *J. Org. Chem.* 59:297 (1994), Burk et al., in *Tetrahedron* 50:4399 (1994), Burk et al, in *J. Am. Chem. Soc.* 115:10125 (1993), Willoughby and Buchwald in *J. Org. Chem.* 58:7627 (1993), or Willoughby and Buchwald in *J. Am. Chem. Soc.* 114:7562 (1992). As yet another alternative, optically pure enantiomers of compounds of Formula I containing a chiral center can be prepared by resolution of a mixture of enantiom rs by selectiv crystallization of a single enantiomer in the presence of an optically pure acid addition salt. Such methods are well known in the art, such as, for example, th preparati n of optically pure

addition salts with each isomer of tartaric acid, tartaric acid derivatives, and the like. Another method which is widely used in the art involves the preparation of diastereomeric derivatives of racemic amines (e.g., α-methoxy-α-(trifluoromethyl) phenylacetic acid (i.e., Mosher's acid) amide derivatives). The resulting diastereomeric derivatives can then be separated by well known techniques, such as chromatography.

The separation of the respective enantiomers of a racemic mixture can be accomplished employing chromatographic techniques which utilize a chiral stationary phase. Examples include chiral gas chromatography (chiral GC), chiral medium performance liquid chromatography (chiral MPLC), chiral high performance liquid chromatography (chiral HPLC), and the like.

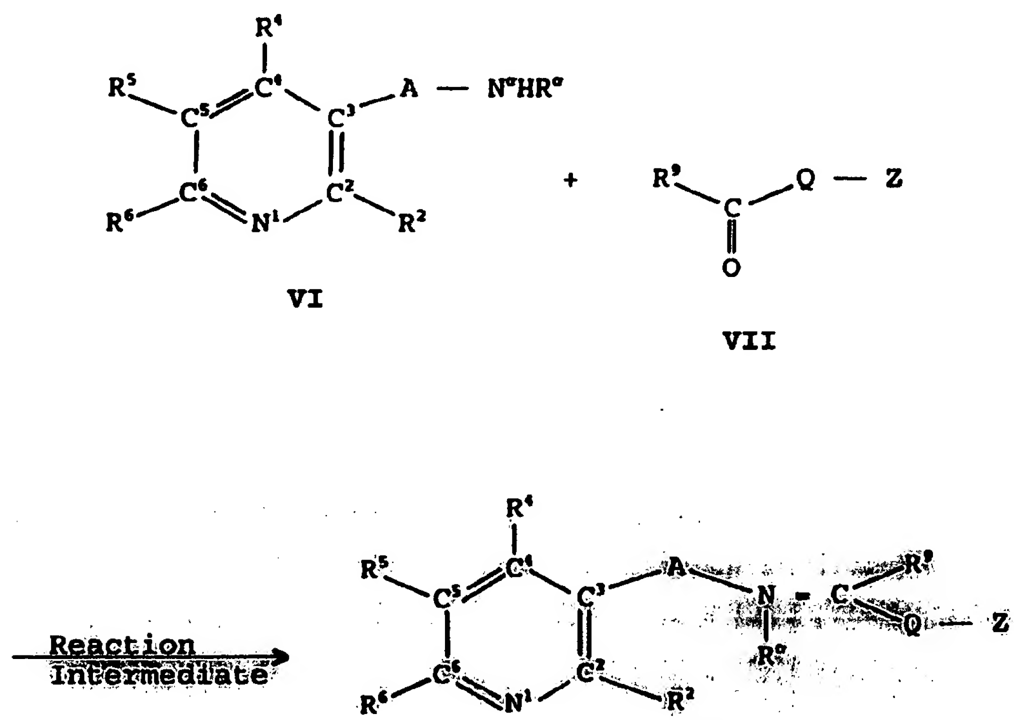
For compounds of Formula I, where R^a is not hydrogen, alkylation step C of Scheme I is carried out. Those of skill in the art can readily identify suitable N-alkylation reactions suitable for such purpose. For example, secondary amine of Formula IV can be contacted with an aldehyde (e.g., formaldehyde, acetaldehyde, benzaldehyde, and the like) in the presence of a suitable reducing agent (such as the reducing agents described above with reference to Step B).

The substituted amines of Formula I produced by the above-described alkylation/reduction reaction can be isolated and purified employing standard methods which are well known in the art (e.g., extraction, chromatography, distillation, and the like). A presently preferred t chniqu for r cov ry f r action product is extraction of amine I fr m basifi d reaction medium with dichloromethane. Alternatively, crude amine can be converted into an acid addition salt (.g., hydrochloride, hydrobromide, fumarat ,

tartrate, and the like), then purified by recrystallization.

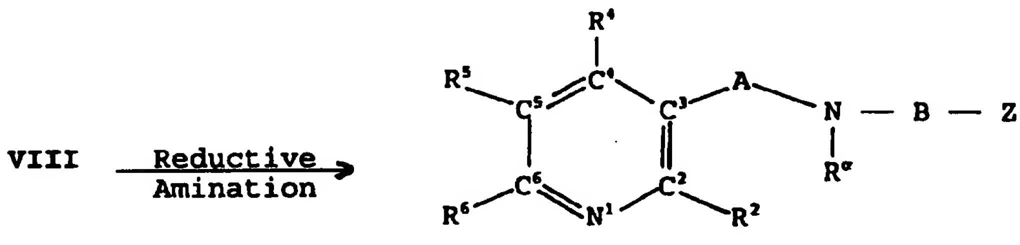
Alternative methods for the preparation of compounds of Formula I are depicted in Schemes II and III, which involve reductive amination, either of ketone **VII** with pyridylamine **VI** (as illustrated in Scheme II), or of pyridylketone **IX** with amine **X** (as illustrated in Scheme III).

<u>Scheme II</u>



VI VII

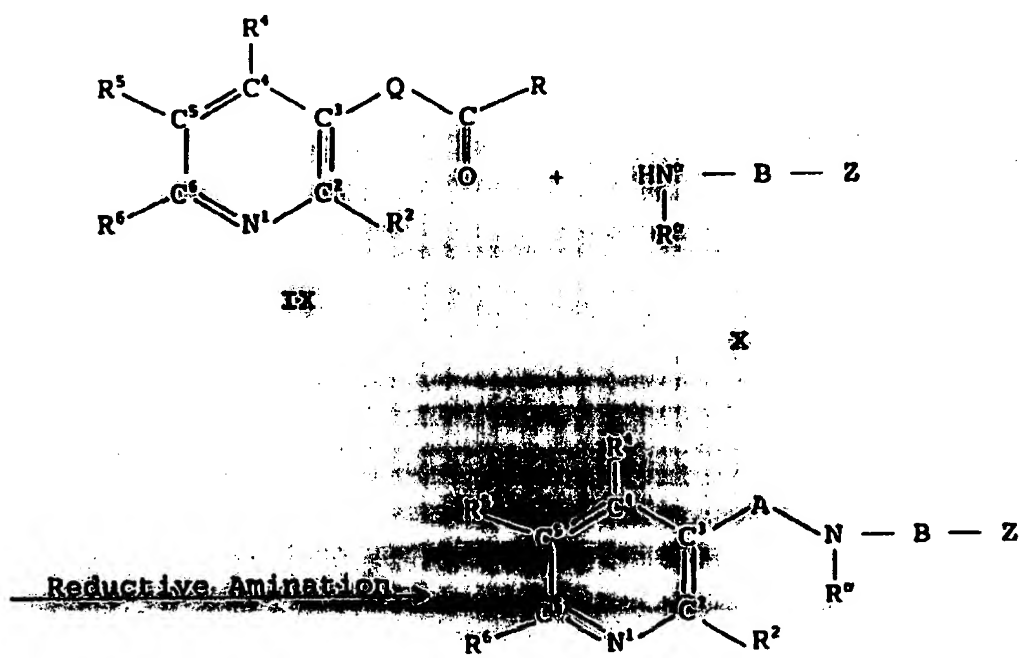
VIII



I

Thus, according to Scheme II, ketone **VII** is coupled with pyridylamine **VI** under reductive conditions which afford I without the need to isolate the intermediate imine **VIII**. In Scheme II, the core of ketone **VII** (i.e., R^9-C(O)-Q-) represents a particular embodiment of B, as defined above. Thus, R^9 and Q are selected such that the moiety "R^9-C(O)-Q-" falls within the definition of B as provided above.

Scheme III



I

Thus, according to Scheme III, pyridylketone **IX** is coupled with amine **X** under reductive conditions which afford **I** without the need to isolate the intermediate imine. In Scheme III, the substituent at C^3 of the pyridine ring of pyridylketone **IX** (i.e., -Q-C(O)-R) represents a particular embodiment of A, as defined above. Thus, Q and R are selected such that the moiety "-Q-C(O)-R" falls within the definition of A as provided above.

The reductive amination coupling reaction referred to in Schemes II and III is well known and can be achieved in a variety of ways. For example, a solution of the appropriate ketone (**VII** or **IX**) and amine (**VI** or **X**), respectively, in suitable solvent (e.g., CH_3OH or acetonitrile) is acidified to a pH of about 3 with suitable acid (e.g., acetic acid), and cooled to about -40°C. After 20 minutes, solid sodium borohydride is added portionwise to the solution. When all of the sodium borohydride has been added, the reaction is allowed to run to completion (over a range of about 30 minutes up to 24 hours, typically for 1-3 hours). The cooling bath is removed and the temperature of the reaction mixture allowed to rise to room temperature.

Aqueous base, such as sodium carbonate, is added to the reaction mixture to increase the pH to about 9-10. Amine product **I** is then isolated by normal solvent extraction procedures and purified by standard means. In some cases, purification is facilitated by conversion of **I** to its acid addition salt (e.g., maleate and fumarate addition salts). A useful alternate reducing agent to sodium borohydride is sodium cyanoborohydride (see Borch, Bernstein and Durst, *J. Amer. Chem. Soc.* 93:2897 (1971)).

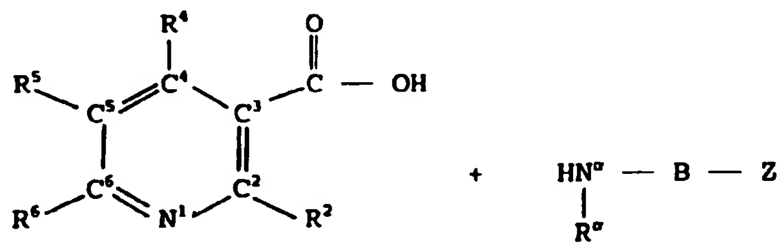
Another versatile reductive amination procedure us s hydrogen as the r ducing ag nt in th pres nce of a transition metal catalyst, such as PtO_2 or Pd/C. As r adily

recognized by those of skill in the art, the choice of reducing agent will often be determined by the presence (or absence) of other functional groups in I.

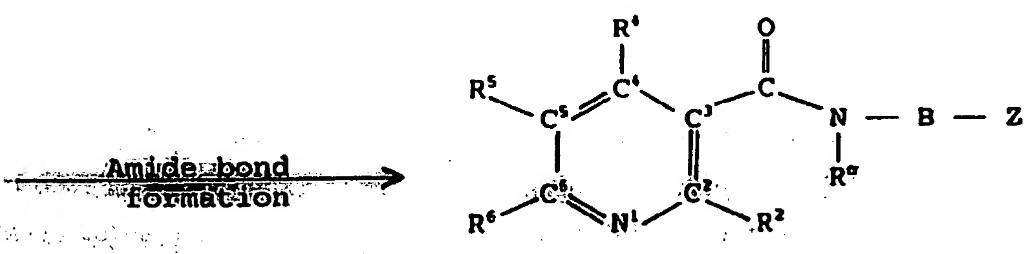
Yet another method for the preparation of compounds of Formula I (specifically compounds wherein A = CH_2) is depicted in Scheme IV, involving reaction of carboxypyridine **XI** with amine **X**, to form an amide, which can then be reduced to produce pyridylamine **XIII**, as follows:

Scheme IV

Step A

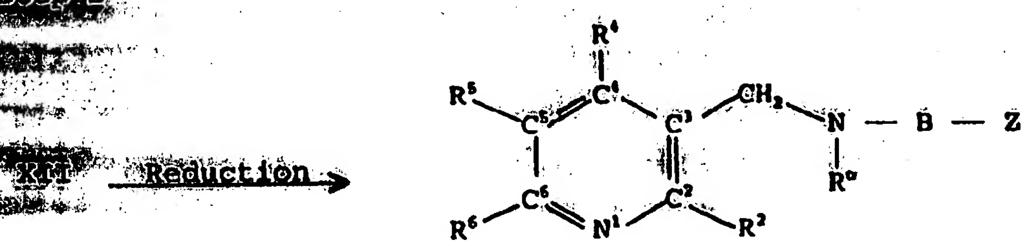


XI **X**



XII

Step B



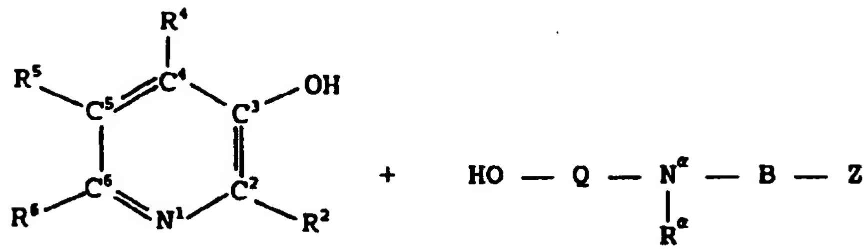
XIII

Thus, according to Scheme IV, compounds d scribed by Formula I in which A = CH_2 can readily be prepared from a variety of nicotinic acid derivatives (**XI**). Referring now to Step A of Scheme IV, amide bond formation between acid **XI** and amine **X** can be accomplished by a variety of well-known procedures. For example, the acid functionality of **XI** can be converted to an acid chloride (for example, by treatment with oxalylchloride), then the resulting acid chloride is contacted with amine **X** in a neutral solvent (e.g., THF or CH_2Cl_2), with or without added base. The resulting amide **XII** can then be purified by standard methods such as chromatography, recrystallization, and the like.

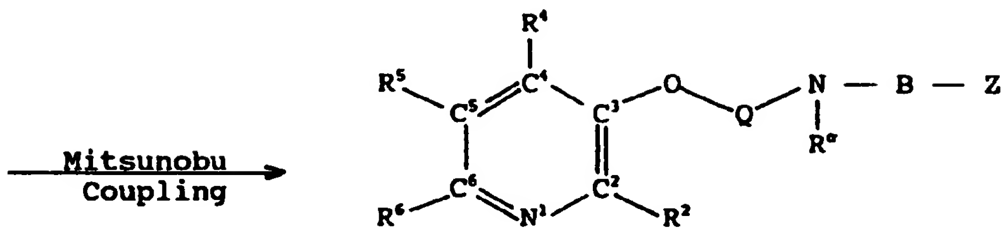
Reduction of the amide functionally in **XII** is typically achieved by the use of a hydride reducing agent, such as, for example, lithium aluminum hydride, diisobutylaluminum hydride, diborane or a diborane complex, and the like. The reaction is typically performed in an aprotic solvent, such as, for example, diethyl ether, THF, hexane, toluene, CH_2Cl_2, and the like, as well as mixtures thereof. Reaction temperatures vary from about -78°C up to solvent reflux, and reaction times vary from about 15 minutes to 24 hours. The choice of reducing agent, solvent, reaction temperature, and reaction time depends upon the presence and nature of other functional groups which may be present in **I**.

Still another method for the preparation of compounds of Formula I is depicted in Scheme V, involving coupling of hydroxypyridine **XIV** with hydroxyamine **XV**, as follows:

Scheme V



XIV XV



XVI

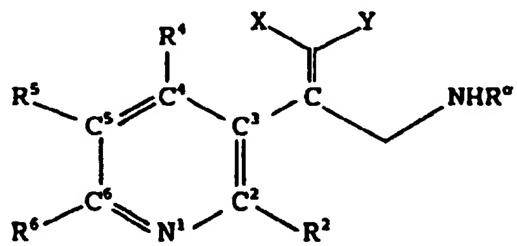
In Scheme V, the preparation of compounds of Formula I having an oxygen atom bridge between the pyridine ring and the side chain is described. Indeed, the use of the Mitsunobu reaction to prepare 3-oxopyridine derivatives has been described in the patent literature (see Abreo et al., WO 94/08992). In Scheme V, the alcohols XIV and XV are dissolved in a suitable solvent (such as, for example, THF) and then treated with triphenylphosphine and diethyl azodicarboxylate at ambient temperature for about 1-24 hours. The reaction product XVI (which is a specific embodiment of I, wherein the moiety "A" of I is represented by "-O-Q-") can readily be isolated and purified as described above.

Yet anoth r method for the preparation of comp unds of F rmula I, specifically compounds in which an exocyclic olefin is present in A, is depicted in Scheme VI, involving r acti n of substitut d pyridin XVII with acid

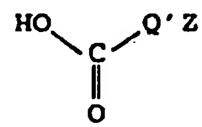
XX, to form amide XVIII, which is then reduced to produce pyridylamine XIX, as follows:

Scheme VI

Step A



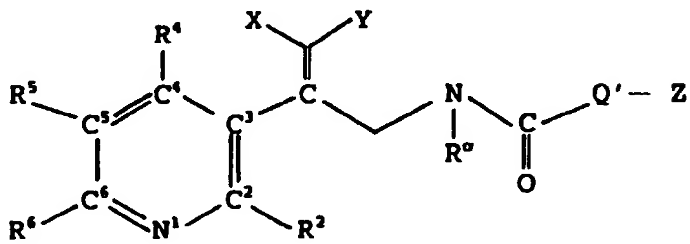
+



XVII

XX

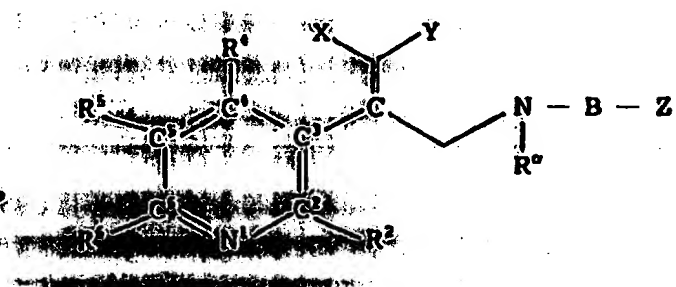
Condensation →



XVIII

Step B

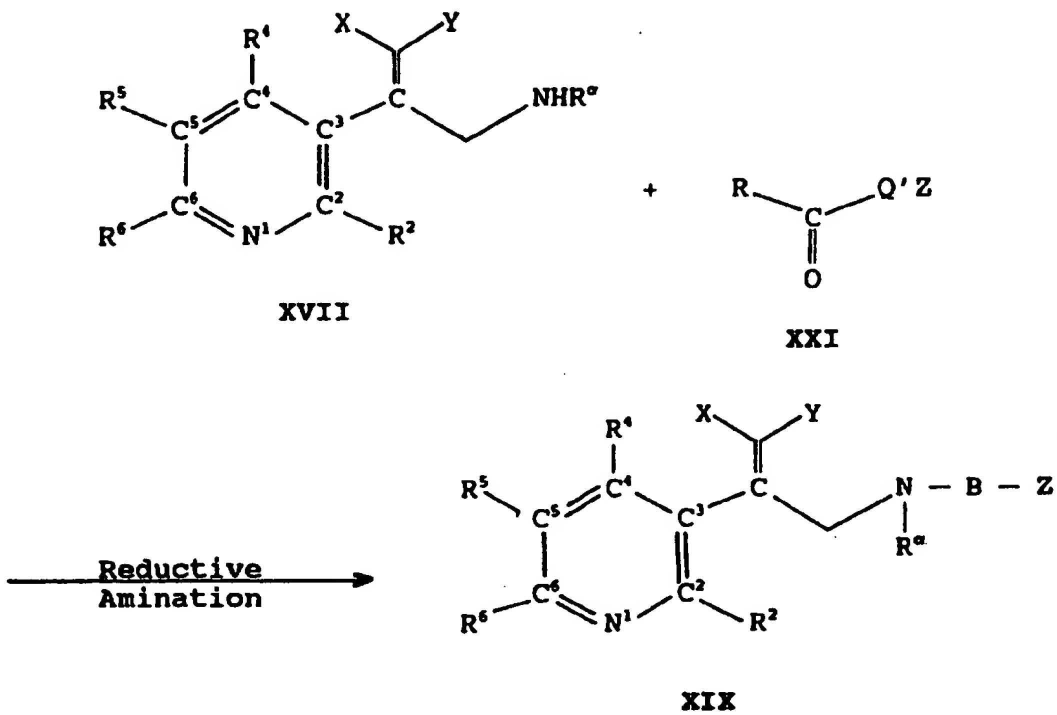
XVIII Reduction →



XIX

Alt rnatively, pyridylamine XIX can be prepared in one step from substituted pyridine XVII by reductive amination of ketone XXI with XVII, as follows:

Scheme VII



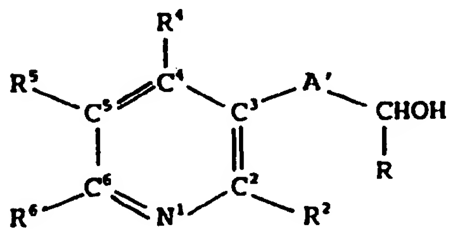
Thus, Schemes VI and VII provide methodolgy for use in the preparation of compounds of Formula **XIX**, i.e., compounds of general formula I which contain an exocyclic double bond as part of moiety A. Synthetic methods useful for the preparation of substituted allylamines **XVII** contemplated for use in the practice of the present invention are known in the art (see, for example, McDonald et al., *J. Med. Chem.* 28:186 (1985); and McDonald et al., *Tetrahedron Letters* 26:3807 (1985)). As shown in Schemes VI and VII, conversion of allylamine **XVII** to Formula I variant **XIX** can be achieved by the reductive amination procedure discussed above with reference to Schemes II and III (see Scheme VII) or by the two step procedure described above with reference to Scheme IV (see Scheme VI).

Yet anoth r meth d for the preparati n of compounds of Formula I is depicted in Scheme VIII, wherein

hydroxypyridine **XXII** is activated with a suitable activating agent, then the resulting activated compound **XXIII** is subjected to nucleophilic displacement conditions in the presence of amine **X**, thereby producing compound **I**.

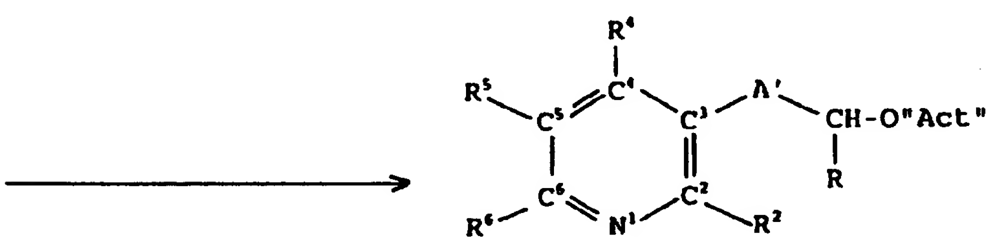
Scheme VIII

Step A



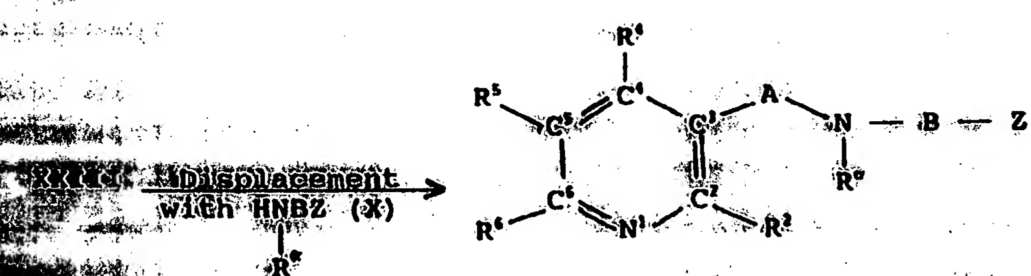
+ Activating agent

XXII



XXIII

Step B



I

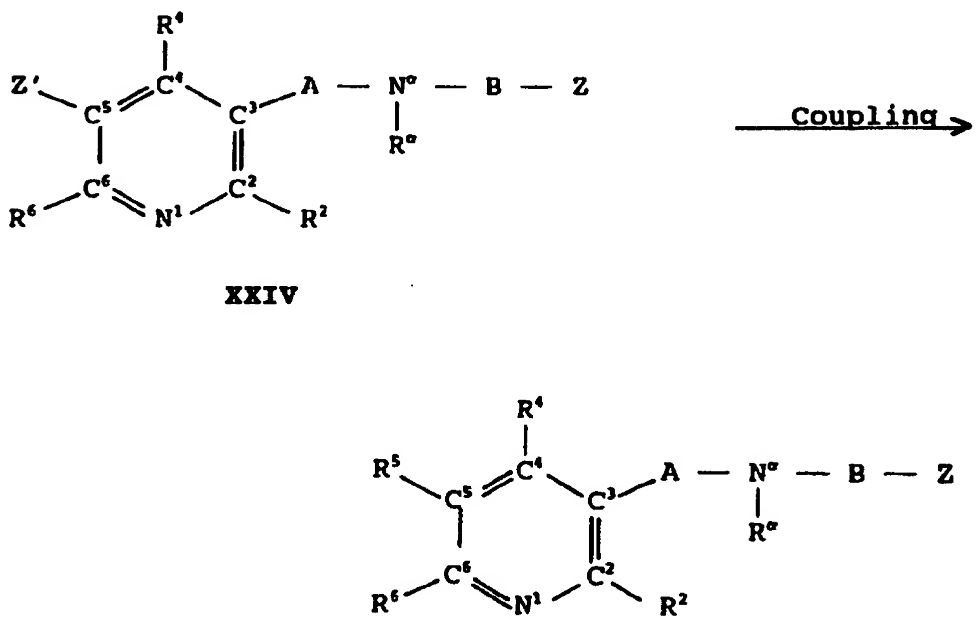
In Schem VIII, starting alcohol **XXII** is select d such that -A'CH(R)- = A in the final product I. Conversion of **XXII** to I can be achieved in some cases by a Mitsunobu reaction (as described above with reference to Scheme V), or, preferably, in two steps incorporating an activation reaction, followed by nucleophilic displacement (assisted by the presence of an activating group "Act"). Suitable activating groups include trifluoroacetate, mesylate, triflate, and the like. Typically, **XXII** is dissolved in an aprotic solvent such as THF at temperatures from -78°C to ambient temperature, usually in the presence of a suitable base such as trialkylamine, especially triethylamine, or 4-dimethylaminopyridine. The anhydride, or chloride derivative of the activating group (e.g., trifluoracetic anhydride, mesylchloride, and the like) is added slowly to the reaction flask. When the addition is complete, the reaction is allowed to proceed at ambient temperature for about 30 minutes up to 12 hours, typically 1 hour. The resulting activated intermediate **XXIII** can be isolated and purified, or used directly without purification in the next step.

Thus, **XXIII** is dissolved in an aprotic polar solvent such as acetonitrile and contacted with amine X. Optionally, a base such as K_2CO_3 or triethylamine is added, which serves to accelerate the reaction. The nucleophilic displacement reaction occurs at about -30°C to 100°C, typically at 25-75°C, and takes from 1-24 hours, typically, 2-8 hours, to reach completion. Product I can then be isolated and purified as described above.

It is readily apparent to those skilled in the art that other activating methodologies can be employed to facilitate the above-described conversion. For example, th hydroxyl group in **XXII** can be converted to a halogen, pr f rably bromine or iodin , prior to the displacement r acti n.

When any one or more of R^2, R^4, R^5 or R^6 of compounds of Formula I are reactive substituents (e.g., bromine, iodine, trifluoromethylsulfonyloxy, and the like), it is possible to further modify such compounds taking advantage of the presence of the reactive functionality. One such modification is shown in Scheme IX.

<u>Scheme IX</u>



XXIV

I

In Scheme IX, the starting material employed is a compound of the Formula XXIV (i.e., a compound according to formula I, wherein R^5 is Z', wherein Z' is an active functionality which is capable of undergoing a transition metal catalyzed coupling reaction (e.g., bromine, iodine, trifluoromethylsulfonyloxy, and the like). If R^5 in the desired final product is an aryl or substituted aryl group, such products can be prepared employing well kn wn organom tallic procedur s, such as, for example, by coupling an arylzinc compound (pr par d by reaction of an arylbr mid with an alkyllithium r agent such as n-

butyllithium, t rt-butyllithium, foll w d by addition of zinc chloride) with compound of Formula I, wherein R^5 is Z' in the presence of a catalytic amount of a suitable coupling catalyst (e.g., $PdCl_2(PPh_3)_2$, and the like) in a suitable solvent such as toluene, dimethylformamide, THF, and the like. Suitable reaction temperatures fall in the range of about 0°C to 140°C (with temperatures in the range of about 0°C up to 80°C being preferred), with reaction times in the range of about 4 up to 24 hours.

Similarly, coupling procedures can be used to prepare compounds of Formula I in which R^2, R^4, R^5 and R^6 are independently alkyl, alkenyl, alkynyl, arylalkyl, alkylaryl, and the like. An alternative method to promote the desired coupling reaction employs organoborane chemistry, wherein arylboronic acids, in the presence of a suitable catalyst (e.g., $Pd(Ph_3)_4$) in basic aqueous dimethoxyethane are coupled with compounds of Formula XXIV wherein one or more of R^2, R^4, R^5 and R^6 is Z'. The reaction is typically carried out at a temperature in the range of about 40°C up to 150°C (with a temperature in the range of 80°C being preferred), for a time in the range of about 1 up to 24 hours (with about 8 hours being preferred). Arylboronic acids are well known in the art and can be readily obtained by those of skill in the art.

It is also readily apparent to those of skill in the art that the selection of a particular reaction scheme will be determined in part by the chemical reactivity of the functional groups in I. Many of the compounds encompassed by Formula I may exist as a variety of geometric isomers, racemic isomers or diasteromeric isomers. It is understood that this invention relates to individual isomers as well as mixtures f isom rs. When individual isom rs are requir d, numerous well known procedures can be employed to either synthesize th desired

isomer in a stereospecific manner, or to separate the isomers at an intermediate or final stage of the synthesis.

The starting materials used in Schemes I-IX are either known compounds and/or can readily be made from known compounds employing well known chemical procedures. For example, the pyridine-containing starting materials can be prepared from appropriately substituted derivatives of nicotinic acid, nicotinamide, pyridine-3-acetic acid, and the like.

In addition to the above-described synthetic procedures, those of skill in the art have access to numerous other synthetic procedures which can be employed for the preparation of invention compounds. Indeed, the literature is replete with methodologies that can be used for the preparation of starting and/or intermediate compounds which are useful for the preparation of invention compounds (e.g., compounds having formulas II, VI, IX, XI, XIV, XVII, XXII, and the like). Such starting and/or intermediate compounds can then be modified, for example, as described herein, to introduce the necessary substituents to satisfy the requirements of Formula I.

In accordance with another embodiment of the present invention, there are provided pharmaceutical compositions comprising pyridine compounds as described above, in combination with pharmaceutically acceptable carriers. Optionally, invention compounds can be converted into non-toxic acid addition salts, depending on the substituents thereon. Thus, the above-described compounds (optionally in combination with pharmaceutically acceptable carriers) can be used in the manufacture of a medicament for modulating the activity of acetylcholine receptors.

Pharmaceutically acceptable carriers contemplated for use in the practice of the present invention include

carriers suitable for oral, intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, inhalation, and the like administration. Administration in the form of creams, lotions, tablets, dispersible powders, granules, syrups, elixirs, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is contemplated.

For the preparation of oral liquids, suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents, and the like.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

Invention compounds can optionally be converted into non-toxic acid addition salts. Such salts are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. R pr sentative salts include th hydrochloride, hydrobromide, sulfat , bisulfat , m thanesulf nate, acetate, oxalate, valerate, oleate, laurat , borate,

benzoate, lactat , phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napsylate, and the like. Such salts can readily be prepared employing methods well known in the art.

In accordance with yet another embodiment of the present invention, there are provided methods of modulating the activity of acetylcholine receptors, said method comprising:

contacting cell-associated acetylcholine receptors with a concentration of a pyridine compound as described above sufficient to modulate the activity of said acetylcholine receptors.

As employed herein, the phrase "modulating the activity of acetylcholine receptors" refers to a variety of therapeutic applications, such as the treatment of Alzheimer's disease and other disorders involving memory loss and/or dementia (including AIDS dementia); cognitive dysfunction (including disorders of attention, focus and concentration), disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia; mood and emotional disorders such as depression, panic, anxiety and psychosis; substance abuse including withdrawal syndromes and substitution therapy; neuroendocrine disorders and dysregulation of food intake, including bulemia and anorexia; disorders of nociception and control of pain; autonomic disorders including dysfunction of gastrointestinal motility and function such as inflammatory bowel disease, irritable bowel syndrome, diarrhea, constipation, gastric acid secreti n and ulcers; pheochromocytoma; cardiovascular dysfunction including hypertension and cardiac arrhythmias, comedication in surgical procedures, and the like.

The compounds of the present invention are especially useful for the treatment of Alzheimer's disease as well as other types of dementia (including dementia associated with AIDS), Parkinson's disease, cognitive dysfunction (including disorders of attention, focus and concentration), attention deficit syndrome, affective disorders, and for the control of pain. Thus modulation of the activity of acetylcholine receptors present on or within the cells of a patient suffering from any of the above-described indications will impart a therapeutic effect.

As employed herein, the phrase "an effective amount", when used in reference to compounds of the invention, refers to doses of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. Such levels typically fall in the range of about 0.001 up to 100 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day being preferred.

The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1
Synthesis of invention pyridine compounds via Synthetic Scheme I

Formation of imine, Method A:

Into a two-necked, round-bottomed flask fitted with a condenser and flushed with nitrogen was placed compound II (wherein R^2, R^4, R^5 and R^6 are each H, and R is H or m thyl), 2.5 ml/mmole of dry dimethyl ether (DME) and 1 to 1.5 q of the liquid amine, NR^aH_2 (wherein R^a is selected fr m cyclopropyl, isopropyl or phenylpropyl). The reaction mixtur was cooled to 0°C and 0.2 t 0.5 eq of a

1M solution of $TiCl_4$ in methylene chloride was added. Aft r stirring for 30 minutes at 0°C, the mixture was allowed to warm to room temperature and stirred for 2 to 6 hours. Then phosphate buffer (4 ml/mmole; pH=6.8) was added and the solution extracted three times with ether. The organic phases were combined, washed with brine, dried ($MgSO_4$) and concentrated under vacuum (15mm Hg) to give a compound pure enough for the reduction step used to prepare the desired product.

Formation of imine, Method B:

Into a two-necked, round-bottomed flask fitted with a dry ice condenser and flushed with nitrogen was placed compound II (wherein R^2, R^4, R^5 and R^6 are each H, and R is H or methyl) and 2.5 ml/mmole of dry dimethyl ether (DME) and cooled to 0°C. An excess of the gaseous amine, $N^aR^aH_2$ (wherein R^a is methyl) was condensed into the reaction mixture and 0.5 eq of 1M $TiCl_4$ in solution in methylene chloride was added. The mixture was warmed up to room temperature and stirred for 2 to 6 hours. Work up was accomplished following the same procedure described in Method A.

α-Methyl-N-methyl-3-picolylimine (Method B):

3-acetylpyridine (4.0g; 33.01 mmole), methylamine (in excess) and $TiCl_4$ (0.3 eq) were stirred for 12 h at room temperature. 4.1g of crude material were obtained, 90% conversion. ^1H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J=2Hz, 1H), 8.96 (dd, J=4Hz and 2Hz, 1H), 8.08 (dt, J=2Hz and 6Hz, 1H), 7.30 (dd, J=6Hz and 4Hz 1H), 3.45 (s, 3H), 2.27 (s, 3H).

α-Methyl-N-isopropyl-3-pic lylimine (Method A)

3-Acetylpyridine (1.0g; 8.26 mmole), isopropylamine (0.54g; 9.90 mmole) and $TiCl_4$ (0.5 eq) were stirred for 3 h at room temperature. 1.1g of crude material were obtained, 90% conversion. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, J=2Hz, 1H), 8.60 (dd, J=2Hz and 5Hz, 1H), 8.09 (dt, J=2Hz and 8Hz, 1H), 7.30 (dd, J=5Hz and 8Hz, 1H), 3.85 (sept, J=6Hz, 1H), 2.26 (s, 3H), 1.22 (d, J=6Hz, 6H).

α-Methyl-N-cyclopropyl-3-picolylimine (Method A)

3-Acetylpyridine (4.0g, 33.04 mmole), cyclopropylamine (2.82g, 49.5 mmole, 1.5 eq) and $TiCl_4$ (0.5 eq) were stirred for 3 h at room temperature. 4.85g of crude material were obtained, 98% conversion. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J=2Hz, 1H), 8.80 (dd, J=2Hz and 5Hz, 1H), 8.24 (dt, J=2Hz and 7Hz, 1H), 7.43 (dd, J=5Hz and 7Hz, 1H), 2.87 (s, 3H), 0.95 (m, 4H).

N-Cyclopropyl-3-picolylimine (Method A)

3-carboxyaldehyde pyridine (6g, 56.01 mmole), cyclopropylamine (4.8g, 84.01 mmole, 1.5 eq) and $TiCl_4$ (0.1 eq) were stirred for 1 h at room temperature. 7.4g of crude material were obtained, 100% conversion, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J=2Hz, 1H), 8.60 (dd, J=2Hz and 5Hz, 1H), 8.06 (dt, J=2Hz and 7Hz, 1H), 7.31 (dd, J=5Hz and 7Hz, 1H), 3.07 (m, 1H), 1.19 (m, 4H).

N-Phenylpropyl-3-picolylimine (Method A)

3-Carboxyaldehyde pyridine (1.0g, 9.33 mmole), 3-phenyl-1-propylamin (1.26g, 9.33 mmole) and $TiCl_4$ (0.1 eq) w re stirred for 3 h at room t mperature. 2.2 g of crude material were obtain d, 95% conversion. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J = 2Hz, 1H), 8.65 (dd, J = 2Hz and

5Hz, 1H), 8.31 (s, 1H), 8.11 (dt, J = 2Hz and 7Hz, 1H), 7.38 - 7.16 (m, 6H), 3.69 (m, 2H), 2.72 (m, 2H), 2.04 (m, 2H).

Reduction of imine to amine, Method C:

Into a one-necked, round-bottomed flask was introduced imine, sodium cyanoborohydride (2 eq), methanol (1ml/mmole) and a trace of bromcresol green indicator. To this blue solution was added dropwise 2M HCl in dioxane such that the yellow end point was barely maintained. The resulting yellow solution was stirred 20 minutes at room temperature followed by addition of 2M HCl in dioxane (half of the quantity used previously). The resulting solution was stirred for one more hour at room temperature and concentrated under reduced pressure. To the resulting crude material was added water (2ml/mmole). The solution was basified with aqueous NaOH (1N) and extracted three times with methylene chloride. The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified via chromatography on silica using $CHCl_3$ or $CHCl_3$/MeOH (99:1) as eluant.

α-Methyl-N-methyl-3-picolylamine (Method C):

α-Methyl-N-methyl-3-picolylimine (0.50g, 3.75 mmole) and $NaBH_3CN$ (2 eq) yielded 264mg of the pure compound (70%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J=2Hz, 1H), 8.50 (dd, J=2Hz and 5Hz, 1H), 7.66 (dt, J=2Hz and 7Hz, 1H), 7.26 (dd, J=5Hz and 7Hz, 1H), 3.70 (q, J=7Hz, 1H), 2.31 (s, 3H), 1.37 (d, J=7Hz, 3H).

90 mg of α-methyl-N-methyl-3-picolylamine was convert d to the dihydrobr mide salt. 160mg of the dihydr bromide product were obtain d, 81% yield. ^1H NMR (300 MHz, CD_3OD) δ 9.11 (s, 1H), 8.9 (d, J=4Hz, 1H), 8.84

(d, J=6Hz, 1H), 8.14 (dd, J=8Hz and 4Hz, 1H), 4.78 (q, J=7Hz, 3H), 2.60 (s, 3H), 1.70 (d, J=7Hz, 3H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 150.2, 149.3, 145.9, 140.1, 131.8, 59.3, 34.3, 20.4; mp: 210-211°C; C, H, N Analysis: $C_8H_{12}N_2$, 2HBr.

α-Methyl-N-isopropyl-3-picolylamine (Method C):

α-Methyl-N-isopropyl-3-picolylimine (0.50g, 3.08 mmole) and $NaBH_3CN$ (1.5 eq) yielded 0.30g of pure compound (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J=2Hz, 1H), 8.49 (dd, J=2Hz and 5Hz, 1H), 7.65 (dt, J=2Hz and 8Hz, 1H), 7.25 (dd, J=5Hz and 7Hz, 1H), 3.94 (d, J=7Hz, 1H), 2.60 (sept, J=6Hz, 1H), 1.35 (d, J=7Hz, 3H), 1.07 (d, J=6Hz, 3H), 0.98 (d, J=6Hz, 3H).

100 mg of α-methyl-N-isopropyl-3-picolylamine was converted to the dihydrobromide salt (134 mg, 68%). ^{1}H NMR (300 MHz, CD_3OD) δ 9.19 (s, 1H), 8.90 (m, 2H) 8.15 (t, J=7Hz, 1H), 4.92 (m, 1H), 3.33 (m, 1H), 1.71 (d, J=7Hz, 3H), 1.31 (d, J=7Hz, 6H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 147.6, 144.0, 143.5, 138.8, 53.3, 50.4, 19.5, 19.4, 19.0; mp = 126-127°C.

α-Methyl-N-cyclopropyl-3-picolylamine (Method C):

α-Methyl-N-cyclopropyl-3-picolylimine (2.43g, 15 mmole) and $NaBH_3CN$ (2 eq) yielded 1.82g of the pure compound (74.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J=2Hz, 1H), 8.50 (dd, J=5Hz and 2Hz, 1H), 7.65 (dt, J=7Hz and 2Hz, 1H), 7.26 (dd, J=2Hz and 5Hz, 1H), 1.39 (d, J=6Hz, 3H), 0.40 (m, 4H).

1.12g of α-methyl-N-cyclopropyl-3-picolylamine was convert d to the fumaric acid salt (0.68 g, 30%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (d, J=2Hz, 1H), 8.47 (dd, J=2Hz and 5Hz, 1H), 7.88 (dt, J=2Hz and 7Hz, 1H), 7.42 (dd, J=5Hz and 7Hz, 1H), 6.60 (s, 3.6H), 4.40 (q, J=6Hz, 1H), 2.38 (m,

1H), 1.57 (d, J=6Hz, 3H), 0.67 (m, 4H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 169.9, 150.7, 135.8, 125.8, 57.9, 29.7, 18.9, 4.32; mp = 144 - 145°C; C, H, N Analysis: $C_{10}H_{14}N_2$ 1.8($C_4H_4O_4$).

N-Cyclopropyl-3-picolylamine (Method C):

N-Cyclopropyl-3-picolylimine (2g, 13.6 mmole) and $NaBH_3CN$ (2 eq) yielded 1.57g of the pure compound (77%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J=2Hz, 1H), 8.50 (dd, J=2Hz and 5Hz, 1H), 7.66 (dt, J=2Hz and 7Hz, 1H), 7.25 (dd, J=5Hz and 7Hz, 1H), 3.82 (s, 2H), 2.11 (m, 1H), 1.91 (brs, 1H) 0.45 (m, 4H).

259 mg of N-cyclopropyl-3-picolylamine was converted to the fumaric acid salt (273 mg, 43%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J=2Hz, 1H), 8.47 (dd, J=2Hz and 5Hz, 1H), 7.86 (dt, J=2Hz and 5Hz, 1H), 7.38 (dd, J=5Hz and 7Hz, 1H), 6.60 (s, 3.4H), 4.20 (s, 2H), 2.61 (m, 1H), 0.73 (m, 4H); mp = 126 - 127°C; C, H, N Analysis: $C_9H_{12}N_2$ 1.7($C_4H_4O_4$).

N-Phenylpropyl-3-picolylamine (Method C):

N-Phenylpropyl-3-picolylimine (2.10g, 9.37 mmole) and $NaBH_3CN$ (2 eq) yielded 1.20g of the pure compound (57%). ^1H NMR (300 MHZ, $CDCl_3$) δ 8.53 (d, J=2Hz, 1H), 8.48 (dd, J=2Hz and 6Hz, 1H), 7.66 (dt, J=2Hz and 7Hz, 1H), 7.31-7.16 (m, 6H), 3.78 (s, 2H), 2.67 (m, 4H), 1.84 (m, 2H).

0.30 g of N-phenylpropyl-3-picolylamine was converted to the fumaric acid salt (0.41 g, 75%). ^1H NMR (300 MHz, CD_3OD) δ 8.54 (d, J=2Hz, 1H), 8.50 (dd, J=6Hz and 2Hz, 1H), 7.85 (dt, J=2Hz and 7Hz, 1H), 7.41 (dd, J=6Hz and 7Hz, 1H), 7.20 - 7.05 (m, 5H), 6.6 (s, 3.2H), 4.15 (s, 2H), 2.96 (m, 2H), 2.61 (m, 2H), 1.91 (m, 2H); mp = 141-142°C; C, H, N Analysis: $C_{15}H_{18}N_2$ 1.6($C_4H_4O_4$).

Alkylation of amine, M thod D:

Into a one-necked, round-bottomed flask was introduced the amine and acetonitrile (10 ml/mmole). To the resulting solution was added formaldehyde (37%) and sodium cyanoborohydride (1.5 to 2 eq). After stirring at 0°C for 30 minutes, acetic acid was introduced and the crude mixture was stirred at room temperature overnight. The resulting solution was concentrated under reduced pressure, the residue was taken into H_2O and basified with NaOH. The aqueous solution was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure, yielding an oil. The crude material was purified via chromatography on silica using $CHCl_3$ in general as eluant.

α-Methyl-N,N-dimethyl-3-picolylamine (Method D):

α-Methyl-N-methyl-3-picolylamine (0.58g, 4.29 mmole), formaldehyde (37%, 1.63 ml), sodium borohydride (0.41g, 6.47 mmole) and acetic acid (200μl) were used. 0.37 g of pure material was obtained (58%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 8.50 (d, J=6Hz, 1H), 8.12 (d, J=7Hz, 1H), 7.64 (dd, J=7Hz and 6Hz, 1H), 3.46 (d, J=6Hz, 1H), 2.21 (s, 6H), 1.38 (d, J=6Hz, 3H).

100 mg of α-methyl-N,N-dimethyl-3-picolylamine was converted to the bromine salt (167 mg, 80%). ^1H NMR (300 MHz, CD_3OD) δ 8.89 (s, 1H), 8.78 (d, J=6Hz, 1H), 8.58 (d, J=8Hz, 1H), 7.95 (dd, J=6Hz and 8Hz, 1H), 4.84 (q, J=7Hz, 1H), 2.25 (s, 6H), 1.78 (d, J=7Hz, 3H); mp = 178-179°C.

N-Methyl-N-cyclopropyl-3-picolylamine:

Into a 100 ml tw -neck d flask fitted with a dr pping funnel and flushed with nitrog n was intr duced

N-cyclopr pyl-3-picolylamine (500mg, 3.37 mmol) and dimethylformamide (10 mL). The reaction mixture was placed in an ice bath and oil free sodium hydride (65.2mg, 2.73 mmole) was added. After 5 minutes the ice bath was removed and the mixture was stirred at room temperature for 10 minutes. Then iodomethane (42mg, 2.96 mmole) was added slowly at 0°C. After an hour, TLC analysis indicated that the reaction was not complete, thus more sodium hydride (13.3mg, 0.54 mmole) and iodomethane (0.1 mL) were added. After 12 h at room temperature, the mixture was hydrolyzed with cold water (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (25 ml), dried ($MgSO_4$), and concentrated under vaccuum (15 mm Hg) to give brown oil (121 mg, 0.745 mmole, 22%).

N-Methyl-N-cyclopropyl-3-picolylamine was converted to the fumaric acid salt (192mg, 0.55 mmole, 74%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.44 (d, J=2Hz, 1H), 8.37 (dd, J=2Hz and 5Hz, 1H), 7.76 (d, J=7Hz, 1H), 7.30 (dd, J=5Hz and 7Hz, 1H), 6.53 (s, 3.2H), 4.02 (s, 2H), 2.48 (s, 3H), 2.20 (m, 1H), 0.51 (m, 4H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 169.3, 151.9, 150.3, 140.9, 135.6, 131.1, 125.4, 59.4, 42.3, 39.8, 6.31; mp = 126 - 127°C; C, H, N Analysis: $C_{10}H_{14}N_2 \cdot 1.6(C_4H_4O_4)$.

N-Methyl-N-phenylpropyl-3-picolylamine (Method D):

N-Phenylpropyl-3-picolylamine (0.60mg, 2.65 mmole), formaldehyde (37%, 1mL), sodium borohydride (0.25g, 3.98 mmole) and acetic acid (122μl) yielded 220mg of pure material (35%).

N-Methyl-N-phenylpropyl-3-picolylamine (180mg, 0.75 mmole) was conv rted to th fumaric acid salt (240 mg, 0.67 mmole, 89%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (s, 1H), 8.52 (d, J=6Hz, 1H), 8.17 (d, J=7Hz, 1H), 7.69 (dd, J=6Hz and 7Hz, 1H), 7.14-6.99 (m, 5H), 6.58 (s, 2H), 3.95 (m,

2H), 2.66 (m, 2H), 2.53 (m, 2H), 2.39 (s, 3H), 1.89 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 169.7, 149.8, 148.5, 142.9, 135.8, 129.5, 128.1, 127.2, 59.1, 57.1, 41.07, 33.8, 28.2; mp = 129 - 130°C.

Example 2

5-Bromo-3-(N-methoxy-N-methyl)pyridinecarboxamide

To a slurry of 5-bromo-3-pyridinecarboxylic acid (22.2 g, 110 mmol) in 1,2-dichloroethane (50 mL), thionyl chloride (24 mL, 330 mmol) was slowly added over a period of 30 min with intermittent cooling in an ice bath to maintain a temperature below 20°C. The reaction was allowed to warm to room temperature, and heated to reflux for 18 h. The reaction mixture was cooled to 10°C, and additional thionyl chloride (4 mL, 50 mmol) was added dropwise. The reaction was warmed to reflux for 6 h, then allowed to cool to room temperature. Residual thionyl chloride and solvent were removed by rotary evaporation followed by high vaccum to provide 5-bromo-3-pyridinecarbacyl chloride hydrochloride as a colorless solid (28.4 g, 100%).

To a suspension of this material in 1,2-dichloroethane (300 mL) at -10°C was added *N,O*-dimethylhydroxylamine hydrochloride (10.73 g, 110 mmol), followed by the dropwise addition of triethylamine (31 mL, 220 mmol). The mixture was stirred at 25°C for 48 h before water (200 mL) was added. The organic phase was separated and the aqueous phase was extracted with chloroform (2 x 50 mL). The combined organic extracts were washed with saturated sodium carbonate solution (50 mL), brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The crud mat rial was chromatograph d on silica gel with ethyl acetat -h xane (1:2) as eluant to afford the titl c mp und as an oil, 25.7 g, 95%. LRMS (EI) m/ 246 ($C_8H_9{}^{81}BrN_2O_2$, M^+), 244 ($C_8H_9{}^{79}BrN_2O_2$, M^+); ^1H NMR ($CDCl_3$, 300

MHz): δ 8.87 (d, J=1.2Hz, 1H), 8.76 (d, J=2.1Hz, 1H), 8.19 (m, 1H), 3.58 (s, 3H), 3.39 (s, 3H).

Example 3
5-Bromo-3-pyridinecarboxaldehyde

5-Bromo-3-(N-methoxy-N-methyl)pyridine carboxamide (25 g, 102 mmol) was dissolved in toluene (250 mL) under inert atmosphere. The resulting mixture was cooled to -10°C with stirring. Diisobutylaluminum hydride (88.4 mL of a 1.5 M solution in toluene, 132.6 mmol) was added, keeping the reaction temperature at -10°C, and after the addition the mixture was stirred at 0°C for 1 h. The solution was again cooled to -10°C and a further 0.2 equivalent of diisobutylaluminum hydride (17 mL of a 1.5 M solution in toluene, 25.5 mmol) was added; stirring was then continued at 0°C for 30 minutes. The reaction mixture was poured into 1 M HCl (500 mL) with stirring and this was cooled to 0°C and the pH adjusted to 10 with NaOH (solid).

The solution was extracted with isopropyl acetate (2 x 500 mL), the combined organic layers washed with water (2 x 250 mL), brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow solid (14.5 g). The combined aqueous fractions were filtered through celite, extracted with isopropyl acetate (2 x 200 mL), the combined organic layers washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a second crop of yellow solid. The crude materials were combined and chromatographed on silica gel with ethyl acetate-hexane (3:7) as eluant to afford the title compound as a solid, 8.75 g, 46%. M.p. 97-98°C; ^1H NMR (DMSO-d_6, 300 MHz): δ 10.08 (s, 1H), 9.06 (bs, 1H), 9.01 (d, J=2Hz, 1H), 8.48 (t, J=2Hz, 1H).

Example 4

5-Bromo-3-(N-pyrrolidinomethyl)pyridine

5-Bromo-3-pyridinecarboxaldehyde (8.75 g, 47 mmol) and pyrrolidine (7.85 mL, 94 mmol) were dissolved in acetonitrile (250 mL) with stirring. The reaction mixture was chilled (0°C), sodium cyanoborohydride (5.92 g, 94 mmol) was added and the mixture stirred at 0°C for 30 minutes. Glacial acetic acid (5 mL) was added dropwise and the mixture stirred at 25°C for 3 h. Water (200 mL) was added and the mixture extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with water (2 x 100 mL), brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was chromatographed on silica gel with methanol-methylene chloride (1:19) as eluant to afford the title compound as an oil, 9 g, 80%. LRMS (EI) m/e 242 (^{81}Br, M^+), 241 (^{81}Br, M^+-H), 240 (^{79}Br, M^+), 239 (^{79}Br, M^+-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.56 (d, J=2Hz, 1H), 8.45 (bs, 1H), 7.87 (s, 1H), 3.61 (s, 2H), 2.52 (bs, 4H), 1.81 (m, 4H).

Example 5

4-Bromophenyl-tert-butyldimethylsilyl ether

4-Bromophenol (5.76 g, 30 mmol), imidazole (4.08 g, 60 mmol) and tert-butyldimethylsilyl chloride (5.02 g, 33 mmol) were stirred in anhydrous DMF (100 mL) at 25°C for 18 h. The reaction mixture was then poured into water (100 mL) and extracted with ethyl acetate (2 x 75 mL). The combined extracts were washed with water (2 x 75 mL), brine (75 mL) and dried ($MgSO_4$) before concentration *in vacuo*. The crude product was chromatographed on silica gel with ethyl acetate:hexane (1:4) as eluant to afford the title compound as an oil, 7.9 g, 92%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (app. dt, J=9Hz, 3Hz and 1Hz, 2H), 6.73 (app. dt, J=9Hz, 3Hz and 1Hz, 2H) 0.98 (s, 9H), 0.21 (s, 6H).

Example 6

4-Bromo-3-chlorophenyl-tert-butyldimethylsilyl ether

Repeating the procedure of Example 5, but using the appropriate starting materials in place of 4-bromophenol, the following compound was obtained:
4-Bromo-3-chlorophenyl-tert-butyldimethylsilyl ether
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, J=2Hz, 1H), 7.24 (dd, J=9Hz and 2Hz, 1H), 6.75 (d, J=9Hz, 1H), 1.02 (s, 9H), 0.22 (s, 6H).

Example 7

5-(4-Hydroxyphenyl)-3-(N-pyrrolidinomethyl)pyridine fumarate

To a stirred solution of 4-bromophenyl-*tert*-butyldimethylsilyl ether (2.14 g, 7.5 mmol) in anhydrous diethyl ether (10 mL) at -78°C under inert atmosphere was slowly added *t*-butyllithium (8.8 mL of a 1.7 M solution in pentane, 15 mmol). This was stirred at -78°C for 30 minutes and zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 mmol) was added. The mixture was allowed to warm to 25°C over 30 minutes before being cannulated into a stirred solution of 5-bromo-3-(N-pyrrolidinomethyl)pyridine (900 mg, 3.7 mmol) and bis(triphenylphosphine)palladium(II) chloride (155 mg, 0.22 mmol) in anhydrous THF (10 mL) at 25°C under inert atmosphere. The reaction mixture was stirred for 18 h before being poured into a saturated solution of potassium sodium tartrate (20 mL).

The solids were removed by filtration, the organic phase separated and the aqueous phase washed with ethyl acetate (2 x 100 mL). Th combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), wat r (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and th s lvents r moved *in vacuo*. The resulting oil was dissolved in

methanol (50 mL) and filtered thr ugh paper to rem ve residual solid catalyst. The filtrate was concentrated under reduced pressure before purification using silica gel column chromatography with ethyl acetate-hexane (1:1) as eluant to afford 5-(4-*tert*-butyldimethylsilyloxyphenyl)-3-(N-pyrrolidinomethyl)pyridine, 1.15 g, 42% as an oil. LRMS (EI) m/e 368 (M^+), 367 (M^+-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (d, J=1.5Hz, 1H), 8.46 (bs, 1H), 7.91 (s, 1H), 7.48 (d, J=8Hz, 2H), 6.92 (d, J=8Hz, 2H), 3.72 (s, 2H), 2.60 (s, 4H), 1.83 (s, 4H), 1.00 (s, 9H), 0.22 (s, 6H).

This material (1.15 g, 3.13 mmol) was dissolved in methanol (20 mL) and cesium fluoride (950 mg, 6.25 mmol) was added. The stirred mixture was heated at reflux for 18 h under inert atmosphere. After cooling the solvent was removed *in vacuo* and the resulting oil was dissolved in ethyl acetate (100 mL). This was washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. The crude material was chromatographed on "flash" silica gel with 5% methanol:ethyl acetate as eluant to afford 5-(4-hydroxyphenyl)-3-(N-pyrrolidinomethyl)pyridine 640 mg, 80%. LRMS (EI) m/e 254 (M^+), 253 (M^+-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.64 (d, J=2Hz, 1H), 8.40 (d, J=2Hz, 1H), 7.76 (t, J=2Hz, 1H), 7.17 (d, J=8Hz, 2H), 6.63 (d, J=8Hz, 2H), 3.73 (s, 2H), 2.67 (s, 4H), 1.87 (s, 4H).

The latter product was converted to the title compound by the addition of one equivalent of fumaric acid to a methanol (15 mL) solution of the free amine at 25°C. After 30 minutes the solvent was removed *in vacuo* and the residue pumped under high vacuum. Trituration with diethyl ether followed by recrystallization from ethyl acetate afforded 5-(4-hydroxyphenyl)-3-(N-pyrrolidinomethyl)-pyridin fumarate, (55%). M.p. 177-179°C (EtOAC); ^{1}H NMR ($DMSO-d_6$, 300 MHz): δ 8.79 (s, 1H), 8.51 (s, 1H), 8.07 (s, 1H), 7.57 (d, J=8Hz, 2H), 6.89 (d, J=8Hz, 2H), 6.58 (s, 2H), 4.05 (s, 2H), 2.89 (s, 4H), 1.84 (s, 4H).

Example 8

5-Substituted-3-(N-pyrrolidinomethyl)pyridines

Repeating the procedure of Example 7, but using the appropriate starting materials in place of 4-bromophenyl-*tert*-butyldimethylsilyl ether, the following 5-substituted-3-(N-pyrrolidinomethyl)pyridine compounds were obtained:

(a) 5-(4-*tert*-Butyldimethylsilyloxy-3-chlorophenyl)-3-(N-pyrrolidinomethyl)pyridine:
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.68 (d, J=2Hz, 1H), 8.50 (d, J=2Hz, 1H), 7.82 (bs, 1H), 7.61 (d, J=2Hz, 1H), 7.37 (dd, J=9Hz and 2Hz, 1H), 6.97 (d, J=9Hz, 1H), 3.68 (s, 2H), 2.54 (s, 4H), 1.82 (s, 4H), 1.05 (s, 9H), 0.26 (s, 6H).

(b) 5-(4-Hydroxy-3-chlorophenyl)-3-(N-pyrrolidinomethyl)pyridine:
LRMS (EI) m/e 290 (^{37}Cl, M^+), 289 (^{37}Cl, M^+-H), 288 (^{35}Cl, M^+), 287 (^{35}Cl, M^+-H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.62 (d, J=3Hz, 1H), 8.44 (d, J=3Hz, 1H), 7.73 (t, J=3Hz, 1H), 7.40 (d, J=2Hz, 1H), 7.09 (dd, J=8Hz and 2Hz, 1H), 6.67 (d, J=8Hz, 1H), 3.74 (s, 2H), 2.68 (s, 4H), 1.88 (s, 4H).

(c) 5-(4-Hydroxy-3-chlorophenyl)-3-(N-pyrrolidinomethyl)pyridine fumarate:
M.p. 192-193°C (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.58 (s, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.49 (s, 1H), 7.31 (d, J=8Hz, 1H), 6.85 (d, J=8Hz, 1H), 6.33 (s, 2H), 3.82 (s, 2H), 2.65 (s, 4H), 1.59 (s, 4H).

Example 9

5-Ethynyl-3-(N-pyrrolidinomethyl)pyridine fumarate

5-Bromo-3-(N-pyrrolidinomethyl)pyridine (1.2 g, 5 mmol), tetrakis(triphenylphosphine)palladium(0) (289 mg, 0.25 mmol), copper(I)iodide (95 mg, 0.5 mmol) and triethylamine (5 mL) were stirred in 1,2-dimethoxyethane (5 mL) at 25°C under inert atmosphere. After 10 minutes, trimethylsilylacetylene (1.4 mL, 10 mmol) was added to the mixture and this was stirred for 18 h. Water (30 mL) and ethyl acetate (50 mL) were added and the organic phase separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and filtered before the solvents were removed *in vacuo*. The resulting oil was chromatographed on silica gel with ethyl acetate-hexane (1:9, 1:4) as eluant to afford 5-trimethylsilylethynyl-3-(N-pyrrolidinomethyl)pyridine, 371 mg, 29%. LRMS (EI) m/e 260 (M^++2), 259 (M^++H), 258 (M^+), 257 (M^+-H); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.58 (d, J=2Hz, 1H), 8.47 (d, J=2Hz, 1H), 7.77 (app. t, J=2Hz, 1H), 3.59 (s, 2H), 2.50 (m, 4H), 1.80 (m, 4H), 0.26 (s, 9H).

5-Trimethylsilylethynyl-3-(N-pyrrolidinomethyl) pyridine (371 mg, 1.4 mmol) and cesium carbonate (100 mg) were dissolved in methanol (10 mL) and heated under reflux for 18 h. After cooling, the solvents were removed *in vacuo* and water (10 mL) was added. The aqueous solution was extracted with ethyl acetate (3 x 10 mL), the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed on silica gel with ethyl acetate-hexane (1:9, 1:4, 1:1) as eluant to afford 5-ethynyl-3-(N-pyrrolidinomethyl)pyridine as an oil, 158 mg, 61%.

This was conv rted to the title compound by the addition f one equivalent of fumaric acid to a methan l

(10 mL) solution of th fr amine at 25°C. After 30 minutes the solvent was removed *in vacuo* and the residue pumped under high vacuum. Trituration with diethyl ether followed by recrystallization from ethyl acetate afforded 5-ethynyl-3-(N-pyrrolidinomethyl)pyridine fumarate. M.p. 148-150°C (decomp., EtOH-EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (s, 1H), 8.62 (s, 1H), 7.97 (s, 1H), 6.60 (s, 4H), 4.50 (s, 1H), 3.99 (s, 2H), 2.82 (s, 4H), 1.81 (s, 4H).

Example 10

5-Phenyl-3-(*N*-methoxy-*N*-methyl)pyridinecarboxamide

5-Bromo-3-(*N*-methoxy-*N*-methyl)pyridinecarboxamide (3.0 g, 12.25 mmol), tributylphenyltin (5.13 g, 14 mmol) and triphenylarsine (428 mg, 1.4 mmol) were dissolved in anhydrous DMF (75 mL) with stirring. Bis(dibenzylideneacetone)palladium (402 mg, 5 mol%) was added, and the mixture was stirred at 65°C for 24 h. Ethyl acetate (100 mL), water (100 mL) and 10% ammonium hydroxide (75 mL) were added to the cooled mixture, which was agitated before filtration through celite. The organic layer was separated and the aqueous phase extracted with ethyl acetate (100 mL). The combined organic extracts were washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate-hexane (2:3) as eluant to afford the title compound as an oil (1.7 g, 57%). LRMS (EI) m/e 243 (M^++H), 242 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.93 (s, 2H), 8.23 (m, 1H), 7.63 (d, J=8Hz, 2H), 7.40-7.55 (m, 3H), 3.60 (s, 3H), 3.43 (s, 3H).

Example 11

5-Phenyl-3-pyridinecarboxaldehyde

5-Phenyl-3-(*N*-methoxy-*N*-methyl)pyridinecarboxamide (1.32 g, 5.45 mmol) was dissolved in THF (30 mL) under inert atmosphere, then cooled to -70°C with stirring. Diisobutylaluminum hydride (11 mL of a 1M solution in cyclohexane, 11 mmol) was added. After addition was complete, the mixture was stirred at -70°C for 2h. Saturated ammonium chloride solution (1 mL) was added to the reaction mixture, followed by water (15 mL) and chloroform (50 mL). The mixture was filtered through celite, the organic phase separated and the aqueous phase again extracted with chloroform (80 mL). The combined organic extracts were washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was chromatographed on silica gel with ethyl acetate-hexane (2:3) as eluant to afford the title compound as an oil, 790 mg, 80%. LRMS (EI) m/e 185 (M^++2), 184 (M^++H), 183 (M^+), 182 (M^+-H); ^1H NMR ($CDCl_3$, 300 MHz): δ 10.20 (s, 1H), 9.08 (d, J=2Hz, 1H), 9.05 (d, J=2Hz, 1H), 8.35 (t, J=2Hz, 1H), 7.63 (m, 2H), 7.45-7.55 (m, 3H).

Example 12

5-Phenyl-3-(*N*-pyrrolidinomethyl)pyridine

5-Phenyl-3-pyridinecarboxaldehyde (400 mg, 2.18 mmol) and pyrrolidine (300 mg, 4.39 mmol) were dissolved in acetonitrile (20 mL) with stirring. The reaction mixture was chilled (0°C), sodium cyanoborohydride (30 mg, 4.4 mmol) was added and the mixture stirred at 0°C for 30 minutes. Glacial acetic acid (0.25 mL) was added dropwise and the mixture stirred at 25°C for 18 h. 1M HCl (10 mL) and methanol (10 mL) were added and the mixture c ncentrat d *in vacuo*. Wat r (20 mL) was add d and th olution basified with solid sodium hydroxide. This was extracted with methylene chlorid (3 x 30 mL) and the

combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was chromatographed on silica gel with ethyl acetate-hexane (2:3) as eluant to afford the title compound as an oil, 360 mg, 70%.

This was converted to the fumarate derivative of the title compound by the addition of one equivalent of fumaric acid to a methanol (10 mL) solution of the free amine at 25°C. After 30 minutes, the solvent was removed *in vacuo* and the residue pumped under high vacuum. Trituration with diethyl ether, followed by recrystallization from ethyl acetate afforded 5-phenyl-3-(*N*-pyrrolidinomethyl)pyridine fumarate; M.p. 126-127°C (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.82 (s, 1H), 8.62 (s, 1H), 8.20 (s, 1H), 7.72 (bs, 2H), 7.50 (bs, 3H), 6.58 (s, 2H), 4.15 (s, 2H), 2.97 (s, 4H), 1.85 (s, 4H).

Example 13
5-Phenyl-3-(*N*-azetidinomethyl)pyridine fumarate

Repeating the procedure of Example 12, but using the appropriate starting materials in place of pyrrolidine the title compound was obtained, i.e., 5-Phenyl-3-(*N*-azetidinomethyl)pyridine fumarate; M.p. 138-139°C (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.86 (s, 1H), 8.58 (s, 1H), 8.12 (s, 1H), 7.72 (bd, J=8Hz, 2H), 7.4-7.5 (m, 3H), 6.58 (s, 2H), 4.11 (s, 2H), 3.70 (bt, J=7Hz, 4H), 2.21 (quintet, J=7Hz, 4H).

Example 14
Radioligand Binding

^{3}H-Nicotine binding to rat cerebral membranes was p rformed according to modifications of the method of Flyn and Mash (*J. Neurochem.* 47:1948 (1986)). ^{3}H-Nicotine (80 ci/mmol; New England Nuclear Corporation, Boston, MA) was

used as the ligand for nicotinic acetylcholine receptor binding assays. All other reagents were purchased from the Sigma Chemical Co. (St. Louis, MO).

Male Sprague-Dawley rats (250 - 400 gm) were sacrificed by decapitation, the brains removed and the cerebral cortex dissected on ice. Synaptic membranes were prepared by homogenizing the cortical tissue in 20 volumes of ice-cold modified Tris buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM EDTA, 1 mM PMSF) with a polytron (20 sec at setting 5-6) followed by centrifugation (15 min at 25,000 x g) at 4°C. The resultant pellet was rehomogenized and centrifuged twice. The final pellet was resuspended in ice-cold assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) at a concentration of membrane equivalent to 1 gm wet weight cortex per 10 ml buffer. After protein determination the final membrane preparation was diluted with buffer to 3 mg protein/ml. This membrane preparation was used in either the fresh state or frozen (-70°C) then thawed.

The binding assay is performed manually using 96-well plates, or using a Biomek automated work station (Beckman Instrument Co.). ^{3}H-Nicotine was diluted in assay buffer to give a final concentration of 1.9 nM. The Biomek automated work station was programmed to automatically transfer 750 µl of assay buffer with ^{3}H-nicotine, 230 µl of membrane preparation and 20 µl of solution containing the compound of interest in assay buffer, DMSO, ethanol:DMSO (1:1) or appropriate vehicle to the 96-well plate. Atropine was added to the incubation buffer at a final concentration of 3 µM to block binding to muscarinic acetylcholine receptor sites. The plates were maintained n ic f r 60 min and the tissue-bound radioactivity was separated from the free by rapid filtration in a Brandel Harvester onto GF/C filt rs presoaked in 0.5% polyethyleneimine for at l ast 2 hr. The filt rs wer

washed with 4x2 ml of ice-cold assay buffer and filters were transferred to vials to which 4 ml of scintillation cocktail was added. The radioactivity was measured in a LS-6500 Beckman Liquid Scintillation Counter in an autodpm mode. Data were analyzed by log-logit transformation or non-linear regression analysis (e.g., employing GraphPad Prism, available from GraphPad Software, San Diego, CA) to give IC_{50} values. Non-specific binding was defined by 10μM cytisine.

The ability of invention compounds to displace ^{3}H-QNB (quinuclidinyl benzilate; 43 Ci/mmol) from muscarinic acetylcholine receptors in rat cerebral membranes was also tested using the above-described method in which ^{3}H-nicotine was replaced with 60 pM ^{3}H-QNB, and atropine was excluded from the incubation buffer.

The results of ^{3}H-nicotine and ^{3}H-QNB binding/displacment assays of several invention compounds are summarized in Table I.

Table I

Compound Tested, Formula I, wherein...	IC_{50} (μM)	
	Nicotine	Quinuclidinyl benzilate
A = CH_2; B and R^a combined = $-CH_2CH_2CH_2-$; Z_2 = not present; R^2, R^4, R^6 = H; R^5 = phenyl	1.2	6.0
A = CH_2; B and R^a combined = $-CH_2CH_2CH_2CH_2-$; Z_2 = not present; R^2, R^4, R^6 = H; R^5 = 3-chloro-4-hydroxyphenyl	0.043	>10
A = $-CH(CH_3)-$; B = CH_2; R^a = CH_3; Z_2 = H; R^2, R^4, R^5, R^6 = H	1.9	Less than 20% displacment of ligand with 100 μM of compound
A = CH_2; B and R^a combined = $-CH_2CH_2CH_2CH_2-$; Z_2 = not present; R^2, R^4, R^6 = H; R^5 = ethynyl	0.041	>100
A = CH_2; B = -(cyclopropyl)-; R^a = H; Z_2 = H; R^2, R^4, R^5, R^6 = H	40	>100
A = CH_2; B = -(cyclopropyl)-; R^a = CH_3; Z_2 = H; R^2, R^4, R^5, R^6 = H	16	>100
A = $-CH(CH_3)-$; B = -(cyclopropyl)-; R^a = H; Z_2 = H; R^2, R^4, R^5, R^6 = H	>100	>100

Compound Tested, Formula I, wherein...	IC_{50} (μM)	
	Nicotine	Quinuclidinyl benzilate
A = CH_2; B and R^a combined = $-CH_2CH_2CH_2CH_2-$; Z_2 = not present; R^2, R^4, R^6 = H; R^5 = phenyl	0.53	11.2
A = CH_2; B and R^a combined = $-CH_2CH_2CH_2CH_2-$; Z_2 = not present; R^2, R^4, R^6 = H; R^5 = p-OH-phenyl	0.082	>10
A = $-CH(CH_3)-$; B = $-CH(CH_3)CH_2-$; R^a = H; Z_2 = H; R^2, R^4, R^5, R^6 = H	19	>100
A = CH_2; B = $-CH_2CH_2CH_2-$; R^a = CH_3; Z_2 = phenyl; R^2, R^4, R^5, R^6 = H	34	36
A = CH_2; B = $-CH_2CH_2CH_2-$; R^a = H; Z_2 = phenyl; R^2, R^4, R^5, R^6 = H	20	29
A = $-CH(CH_3)-$; B = CH_2; R^a = H; Z_2 = H; R^2, R^4, R^5, R^6 = H	3.6	>100

As evidenced by the IC_{50} values in the Table, each of the compounds tested was able to displace acetylcholine receptor ligands from their binding sites in rat cerebral membranes.

Example 15
Neurotransmitter Release

Measurement of ^{3}H-dopamine release from rat striatal slices was performed according to the method of Sacaan et al. (*J. Neurochem.* 59:245 (1992)). Male Sprague-Dawley rats (250-300 g) were decapitated and the striata or olfactory tubercles dissected quickly on a cold glass surface. The tissue was chopped to a thickness of 300 μm with a McIlwain tissue chopper. After chopping again at right angles the tissue was dispersed and incubated for 10 min. at 37°C in oxygenated Kreb's buffer. ^{3}H-Dopamine (40 Ci/mmol, NEN- Dupont, Boston, Ma) was added (50 nM) and the tissue was incubated for 30 min. in Kreb's buffer containing 10 μM pargyline and 0.5 mM ascorbic acid. Aliquots of the minced tissue were then transferred to chambers of a Brandel Superfusion system in which the tissue was supported on Whatman GF/B filter discs. The tissue was then superfused with buffer at a constant flow rate of 0.3 ml/min by means of a Brandel peristaltic pump. The perfusate was collected in plastic scintillation vials in 3-min fractions, and the radioactivity was estimated by scintillation spectrophotometry. The superfusate for the first 120 min was discarded. After two baseline fractions had been collected, the superfusion buffer was switched to fresh buffer with or without compound of interest. At the end of the experiment the filter and the tissue were removed, and the radiolabeled neurotransmitter content was estimated after extraction into scintillation fluid. The fractional efflux of radiolabeled neurotransmitter was estimated as the amount of radioactivity in the perfusate fraction relative to the total amount in the tissue.

Following essentially the same procedure as set forth in the preceding paragraph, the amount of ^{3}H-norepinephrine released from rat hippocampus, thalamus and prefrontal cortex slices superfused with buffer containing (or lacking) compounds of interest was also measured.

The results of studies of the effects of an invention compound (as compared to the effect of nicotine) on the release of neurotransmitters from rat brain slices are presented in Table II. The results presented in the Table are expressed as the percent fractional release.

Table II

Ligand-stimulated ^{3}H-neurotransmitter Release *In Vitro* from Slices of Different Rat Brain Regions

Ligand or Compound Tested, Formula I, wherein...	^{3}H-Dopamine Striatum	^{3}H-Norepinephrine Hippocampus	^{3}H-Norepinephrine Thalamus	^{3}H-Norepinephrine Prefrontal Cortex	^{3}H-Dopamine Olfactory Tubercles
Nicotine	2.3±0.7[a]	8.2±1.5[b]	1.7±0.2[c]	2.2±0.2[b]	2.7±0.4[c]
A = CH_2; B and R^{α} combined = $-CH_2CH_2CH_2CH_2-$; Z not present; R^2, R^4 and R^8 = H; and R^6 = 3-chloro-4-[illegible]	6.00	1.91	1.44	1.82	8.75
A = CH_2; B and R^{α} combined = $-CH_2CH_2CH_2CH_2-$; Z not present; [illegible] and R^8 = H; and R^6 = [illegible]	2.09	0.97	0.67	0.84	0.91
A = CH_2; B and R^{α} combined = $-CH_2CH_2CH_2CH_2-$; Z not present; [illegible] and R^8 = H; and R^6 = phenyl	2.48	0.74	1.42	1.43	3.68
A = CH_2; B and R^{α} combined = $-CH_2CH_2CH_2CH_2-$; Z not pres nt; R^2, R^4 and R^8 = H; and R^6 = 4-OH-phenyl	4.32	1.06	2.36	1.24	6.12

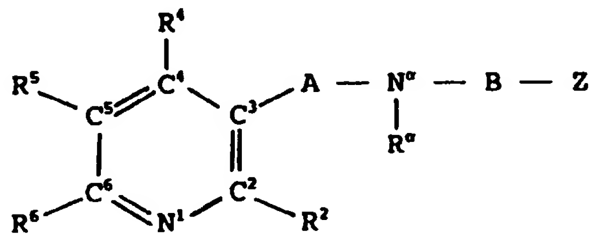
[a] Nicotine concentration 10 μM
[b] Nicotine concentration 300 μM
[c] Nicotine concentration 100 μM.

As shown in Table II, invention compound selectively induces release of catecholamines in different brain regions.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A compound having the structure:



I

wherein:

A is a 1, 2, 3, 4, 5 or 6 atom bridging species linking C^3 of the pyridine ring with N^α,

wherein A is selected from a straight chain or branched chain alkylene moiety having up to six atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to six atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to six atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moiety; provided, however, that any heteroatom contained in A is separated from N^α by at least two carbon atoms; and further provided that when A is a -C(O)- or -C(S)- containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety of A and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety,

wherein A and B can optionally combine to form a monocyclic ring containing A, N^α and B, wherein at least on m thylen unit

intervenes b tween such ring and C^3 of the pyridine ring;

B is a 1, 2, 3 or 4 atom bridging species linking N^α with Z,

wherein B is selected from a straight chain or branched chain alkylene moiety having up to four atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to four atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to four atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, $-N^\beta(R^\beta)-$, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moiety, wherein R^β is hydrogen or a lower alkyl moiety; provided, however, that any heteroatom contained in B is separated from N^α by at least 2 carbon atoms, and further provided that when B is a -C(O)- or -C(S)-containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety, and

wherein B and R^α can optionally combine to form a monocyclic ring containing B, R^α and N^α;

Z is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl,

heterocyclic, substituted heterocyclic, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl, or $-OR^z$, wherein R^z is hydrogen, lower alkyl or aryl, or

Z is not present when A and B cooperate to form a ring containing A, N^α and B, or when R^α and B cooperate to form a ring containing B, R^α and N^α;

R^α is selected from hydrogen or lower alkyl; and

R^2, R^4, R^5 and R^6 are each independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$, $-S(O)_2OR'$ or $-S(O)_2NHR'$, wherein each R' is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl; provided, however, that when R^2, R^4, R^5 or R^6 is $-S(O)R'$, R' is not hydrogen; and further provided that when R' is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom;

$-C(O)R''$, wherein R'' is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalk nyl, substituted arylalkenyl, arylalkynyl,

substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

-OR''' or -NR'''$_2$, wherein each R''' is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the -OR''' or -NR'''$_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

-SiR'''''$_3$, wherein R''''' is selected from alkyl or aryl;

provided, however, that the following compounds are excluded from the definition of Formula I: compounds

wher in A is $-CH{=}CH-(CH_2)_{1\text{-}5}-CH_2-$, B is alkyl, Z is H r absent, R^α is H, and each of R^2, R^4, R^5 and R^6 are independently alkyl or halo; compounds wherein A is $-(CH_2)_{1\text{-}5}-$, B and R^α combine to form a B, R^α, N^α ring such that B and R^α together are C_4R_8 or C_5R_{10}, wherein R is hydrogen or alkyl, and Z is absent; compounds wherein A is $-C(O)-(CH_2)_{1\text{-}5}-$, B is alkyl, Z is absent or H, R^α is H or alkyl, and each of R^2, R^4, R^5 and R^6 are alkyl or halo; compounds wherein A is $-CH_2-$, B is $-CH_2-$ or $-CH_2-CH_2-$, Z is H, R^α is $-CH_3$ or $-CH_2-CH_3$, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-$, B is $-CH_2-CH(CH_3)-CH_2-R$, wherein R is *para-tertiary*butylphenyl, Z is absent, R^α is CH_3 or butyl, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-(CHR)_n$, wherein R is H or alkyl and n = 0 or 1, B is $-(CH_2)_n-CHR-CH(X)-$, wherein R is H, methyl or ethyl, X is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), and n = 0 or 1, Z is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), R^α is H or alkyl, and each of R^2, R^4, R^5 and R^6 are selected from hydrogen, alkyl or alkenyl; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-$, $-CH_2-C_6H_4-$ or $-CH_2-C_{10}H_6-$, Z is hydrogen, $-C_6H_5$, or $-C_{10}H_7$, R^α is CH_3, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-(CH_2)-$, Z is hydrogen, R^α is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-CH_2-[2,3-(OR)_2C_6H_3]$, wherein R is methyl or benzyl, and R^α is hydrogen, or B and R^α combine to form a B, R^α, N^α ring such that B and R^α together are $-C(=CH_2)-[1,2-(3,4(OR)_2benzo]-CH_2CH_2-$, wherein R is methyl or benzyl, Z in all instances is absent, and each of R^2, R^4, R^5 and R^6 are hydrogen; as well as compounds wherein A is $-CH(CH_3)-$ or $-CH_2-CH_2-CH_2-$, B is $-CH_2-CH_2-CH(C_6H_5)-$ or $-CH(CH_3)-C_6H_5$, Z is phenyl or absent, R^α is hydrog n, and ach of R^2, R^4, R^5 and R^6 are hydrogen.

2. A compound according to claim 1 wherein A is selected from:

$-CR^A{}_2-$, wherein each R^A is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl;

-(cycloalkyl)-, or

$-C(=CXY)-CH_2-$, wherein X and Y are each independently selected from hydrogen, lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, halogen, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, aryloxyalkyl, or $-OR^{AA}$, wherein R^{AA} is lower alkyl or aryl.

3. A compound according to claim 2 wherein X and Y are not both $-OR^{AA}$.

4. A compound according to claim 1 wherein A and B combine to form a ring including A, N^α and B.

5. A compound according to claim 4 wherein the combination of A and B is selected from $-O-CH_2CH(CH_2)_n-$, wherein n falls in the range of 1 up to 4.

6. A compound according to claim 1 wherein B is selected from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2-C(O)-$, $-CH_2CH_2C(O)NH-$, $-CH_2CH(CH_3)-$, or $-CH_2-C\equiv C-$.

7. A compound according to claim 1 wherein B and R^α combine to form a ring including R^α, N^α and B.

8. A compound according to claim 7 wherein the combination of B and R^{α} is selected from $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2CH_2-$.

9. A compound according to claim 1 wherein R^{α} is hydrogen or methyl.

10. A compound according to claim 1 wherein R^2 is hydrogen.

11. A compound according to claim 1 wherein R^4 is selected from hydrogen, aryl, alkoxy or aryloxy.

12. A compound according to claim 1 wherein R^5 is selected from alkynyl, aryl, substituted aryl, trialkylsilyl, arylalkyl, arylalkenyl or arylalkynyl.

13. A compound according to claim 1 wherein R^6 is selected from hydrogen, chlorine, amino, methyl or alkoxy.

14. A compound according to claim 1 wherein said compound is substantially optically pure.

15. A compound according to claim 1 wherein said compound is a racemic mixture or a diasteromeric mixture.

16. A compound according to claim 1 wherein:
A = $-CH_2-$,
B and R^{α} combined = $-CH_2CH_2CH_2CH_2-$,
Z = not present,
R^2, R^4, and R^6 = hydrogen, and
R^5 = phenyl.

17. A c mpound according to claim 1 wherein:
$A = -CH_2-$,
B and R^a combined $= -CH_2CH_2CH_2CH_2-$,
Z = not present,
R^2, R^4, and R^6 = hydrogen, and
R^5 = parahydroxyphenyl.

18. A compound according to claim 1 wherein:
$A = -CH_2-$,
B and R^a combined $= -CH_2CH_2CH_2CH_2-$,
Z = not present,
R^2, R^4, and R^6 = hydrogen, and
R^5 = 3-chloro-4-hydroxyphenyl.

19. A compound according to claim 1 wherein:
$A = -CH_2-$,
B and R^a combined $= -CH_2CH_2CH_2CH_2-$,
Z = not present,
R^2, R^4, and R^6 = hydrogen, and
$R^5 = -C{\equiv}C-H$.

20. A compound according to claim 1 wherein:
$A = -CH_2-$,
B and R^a combined $= -CH_2CH_2CH_2-$,
Z = not present,
R^2, R^4, and R^6 = hydrogen, and
R^5 = phenyl.

21. A compound according to claim 1 wherein:
$A = -CH(CH_3)-$,
$B = -CH_2-$,
Z = hydrogen,
R^a = methyl, and
R^2, R^4, R^5 and R^6 = hydrogen.

22. A compound according to claim 1 wherein:
$A = -C(CH_3)_2-$,
$B = -CH_2-$,
Z = hydrogen,
R^a = methyl, and
R^2, R^4, R^5 and R^6 = hydrogen.

23. A compound according to claim 1 wherein:
A = -(spirocyclopropyl)-,
$B = -CH_2-$,
Z = hydrogen,
R^a = methyl, and
R^2, R^4, R^5 and R^6 = hydrogen.

24. A compound according to claim 1 wherein:
$A = -CH_2CH_2-$,
B and R^a combined = $-CH_2CH_2CH_2CH_2-$,
Z = not present, and
R^2, R^4, R^5 and R^6 = hydrogen.

25. A compound according to claim 1 wherein:
A = $-C(=CXY)CH_2-$, wherein X and Y are each independently selected from hydrogen, lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, halogen, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, aryloxyalkyl, or $-OR^{AA}$, wherein R^{AA} is lower alkyl or aryl,
B and R^a combined = $-CH_2CH_2CH_2CH_2-$,
Z = not pr sent, and
R^2, R^4, R^5 and R^6 = hydrogen.

26. A compound according to claim 25 wherein X and Y are not both $-OR^{AA}$.

27. A compound according to claim 1 wherein:
A = $-CH_2-$,
B = $-CH_2CH_2-$,
Z = 3,4-benzopyrrolidine,
R^a = methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

28. A compound according to claim 1 wherein:
A and B combined = $-O-CH_2CHCH_2CH_2CH_2-$, thereby forming a ring including A, N^a and B,
Z = not present,
R^a = methyl, and
R^2, R^4, R^5, and R^6 are independently selected from the group set forth above, with the proviso that R^2, R^4, R^5, and R^6 are not hydrogen, alkyl, alkoxy or halogen.

29. A compound according to claim 1 wherein:
A = $-CH_2-$,
B = $-CH_2-C\equiv C-$,
Z = hydrogen,
R^a = methyl,
R^2, R^4, R^5, and R^6 = hydrogen.

30. A compound according to claim 1 wherein:
A = $-CH_2CH(CH_3)-$,
B = $-CH_2-C\equiv C-$,
Z = hydrogen,
R^a = methyl,
R^2, R^4, R^5, and R^6 = hydrogen.

31. A compound according to claim 1 wherein:

A = $-CH_2-$,

B = $-CH_2-CH{=}C(X)-$, wherein X is selected from hydrogen, lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, halogen, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, aryloxyalkyl, or $-OR^x$, wherein R^x is lower alkyl, or aryl,

Z = lower alkyl, hydroxyalkyl, cyano, trifluoromethyl, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, aryl, sulfonamide, aryloxyalkyl, or $-OR^z$, wherein R^z is lower alkyl or aryl,

R^a = methyl, and

R^2, R^4, R^5, and R^6 = hydrogen.

32. A compound according to claim 31, with the proviso that when X is $-OR^x$, Z is not $-OR^z$.

33. A compound according to claim 1 wherein:

A = $-CH_2-$,

B = $-CH_2CH_2-$,

Z = phenyl or substituted phenyl,

R^a = methyl, and

R^2, R^4, R^5, and R^6 = hydrogen.

34. A compound according to claim 1 wh rein:
$A = -CH_2-$,
$B = -CH_2CH_2-$,
Z = furanyl or substituted furanyl,
R^a = methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

35. A compound according to claim 1 wherein:
$A = -CH_2-$,
$B = -CH_2CH_2-$,
Z = imidazolyl,
R^a = methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

36. A compound according to claim 1 wherein:
$A = -CH_2-$,
$B = -CH_2CH_2-C(O)-$,
Z = phenyl or substituted phenyl,
R^a = methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

37. A compound according to claim 1 wherein:
$A = -CH(CH_3)-$,
$B = -CH_2-$,
Z = hydrogen,
R^a = hydrogen or methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

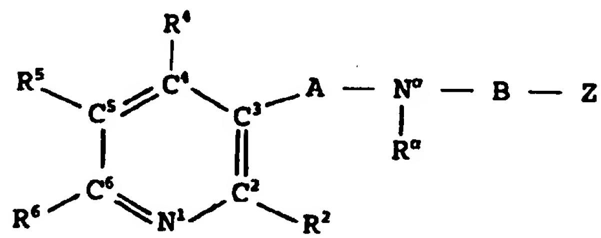
38. A compound according to claim 1 wherein:
$A = -CH(CH_3)-$,
$B = -CH(CH_3)CH_2-$,
Z = hydrogen,
R^a, R^2, R^4, R^5, and R^6 = hydrogen.

39. A compound according to claim 1 wherein:
$A = -CH(CH_3)-$,
$B = -(\text{cyclopropyl})-$,
Z = hydrogen,
R^α, R^2, R^4, R^5, and R^6 = hydrogen.

40. A compound according to claim 1 wherein:
$A = -CH_2-$,
$B = -(\text{cyclopropyl})-$,
Z = hydrogen,
R^α = hydrogen or methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

41. A compound according to claim 1 wherein:
$A = -CH_2-$,
$B = -CH_2CH_2CH_2-$,
Z = phenyl,
R^α = hydrogen or methyl, and
R^2, R^4, R^5, and R^6 = hydrogen.

42. A pharmaceutical composition comprising a compound of the structure:



I

wherein:

A is a 1, 2, 3, 4, 5 or 6 atom bridging species linking C^3 of the pyridine ring with N^α,

wherein A is selected from a straight chain or branched chain alkylene moiety having up to six atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to six atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to six atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, -S-, -S(O)- and/or $-S(O)_2-$ containing alkylene moiety, provided, however, that any heteroatom contained in A is separated from N^α by at least two carbon atoms, and further provided that when A is a -C(O)- or -C(S)- containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety of A and N^α, and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety,

wherein A and B can optionally combine to form a monocyclic ring containing A, N^α and B, wh rein at least one methylen unit

int rvenes between such ring and C^3 of th pyridine ring;

B is a 1, 2, 3 or 4 atom bridging species linking N^α with Z,

wherein B is selected from a straight chain or branched chain alkylene moiety having up to four atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to four atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to four atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, $-N^\beta(R^\beta)-$, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moiety, wherein R^β is hydrogen or a lower alkyl moiety; provided, however, that any heteroatom contained in B is separated from N^α by at least 2 carbon atoms, and further provided that when B is a -C(O)- or -C(S)- containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety, and

wherein B and R^α can optionally combine to form a monocyclic ring containing B, R^α and N^α;

Z is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substitut d aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl,

heterocyclic, substituted heterocyclic, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl, or $-OR^z$, wherein R^z is hydrogen, lower alkyl or aryl, or

Z is not present when A and B cooperate to form a ring containing A, N^α and B, or when R^α and B cooperate to form a ring containing B, R^α and N^α;

R^α is selected from hydrogen or lower alkyl; and

R^2, R^4, R^5 and R^6 are each independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$, $-S(O)_2OR'$ or $-S(O)_2NHR'$, wherein each R' is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl; provided, however, that when R^2, R^4, R^5 or R^6 is $-S(O)R'$, R' is not hydrogen; and further provided that when R' is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom;

$-C(O)R''$, wherein R'' is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substitut d alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl,

substitut d arylalkynyl, h terocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

-OR''' or -NR'''$_2$, wherein each R''' is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the -OR''' or -NR'''$_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

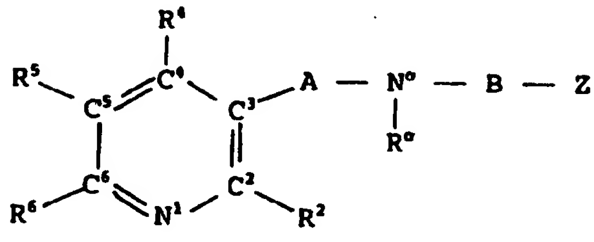
-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

-SiR'''''$_3$, wherein R''''' is selected fr m alkyl or aryl;

pr vided, howev r, that the f llowing compounds are excluded from the definiti n of F rmula I: comp unds

wherein A is $-CH=CH-(CH_2)_{1-5}-CH_2-$, B is alkyl, Z is H or absent, R^a is H, and each of R^2, R^4, R^5 and R^6 are independently alkyl or halo; compounds wherein A is $-(CH_2)_{1-5}-$, B and R^a combine to form a B, R^a, N^a ring such that B and R^a together are C_4R_8 or C_5R_{10}, wherein R is hydrogen or alkyl, and Z is absent; compounds wherein A is $-C(O)-(CH_2)_{1-5}-$, B is alkyl, Z is absent or H, R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are alkyl or halo; compounds wherein A is $-CH_2-$, B is $-CH_2-$ or $-CH_2-CH_2-$, Z is H, R^a is $-CH_3$ or $-CH_2-CH_3$, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-$, B is $-CH_2-CH(CH_3)-CH_2-R$, wherein R is *para-tertiary*butylphenyl, Z is absent, R^a is CH_3 or butyl, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-(CHR)_n$, wherein R is H or alkyl and n = 0 or 1, B is $-(CH_2)_n-CHR-CH(X)-$, wherein R is H, methyl or ethyl, X is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), and n = 0 or 1, Z is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are selected from hydrogen, alkyl or alkenyl; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-$, $-CH_2-C_6H_4-$ or $-CH_2-C_{10}H_6-$, Z is hydrogen, $-C_6H_5$, or $-C_{10}H_7$, R^a is CH_3, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-(CH_2)-$, Z is hydrogen, R^a is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-CH_2-[2,3-(OR)_2C_6H_3]$, wherein R is methyl or benzyl, and R^a is hydrogen, or B and R^a combine to form a B, R^a, N^a ring such that B and R^a together are $-C(=CH_2)-[1,2-(3,4(OR)_2benzo]-CH_2CH_2-$, wherein R is methyl or benzyl, Z in all instances is absent, and each of R^2, R^4, R^5 and R^6 are hydrogen; as well as compounds wherein A is $-CH(CH_3)-$ or $-CH_2-CH_2-CH_2-$, B is $-CH_2-CH_2-CH(C_6H_5)-$ or $-CH(CH_3)-C_6H_5$, Z is phenyl or absent, R^a is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen.

43. Use of a compound having the structure:



I

wherein:

A is a 1, 2, 3, 4, 5 or 6 atom bridging species linking C^3 of the pyridine ring with N^α,

wherein A is selected from a straight chain or branched chain alkylene moiety having up to six atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to six atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to six atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, -S-, -S(O)- and/or $-S(O)_2-$containing alkylene moiety; provided, however, that any heteroatom contained in A is separated from N^α by at least two carbon atoms; and further provided that when A is a -C(O)- or -C(S)- containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety of A and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety;

wherein A and B can optionally combin to form a monocyclic ring containing A, N^α and B, wherein at l ast one methylene unit

interven s betw en such ring and C^3 of th pyridine ring;

B is a 1, 2, 3 or 4 atom bridging species linking N^α with Z,

wherein B is selected from a straight chain or branched chain alkylene moiety having up to four atoms in the backbone thereof, or a substituted alkylene moiety, a straight chain or branched chain alkenylene moiety having up to four atoms in the backbone thereof, or a substituted alkenylene moiety, an alkynylene moiety having up to four atoms in the backbone thereof, or a substituted alkynylene moiety, -O-, -C(O)-, -C(S)-, $-N^\beta(R^\beta)-$, -S-, -S(O)- and/or $-S(O)_2$-containing alkylene moiety, wherein R^β is hydrogen or a lower alkyl moiety; provided, however, that any heteroatom contained in B is separated from N^α by at least 2 carbon atoms, and further provided that when B is a -C(O)- or -C(S)-containing alkylene moiety, at least one methylene unit intervenes between the -C(O)- or -C(S)- moiety and N^α; and further provided that N^α is not conjugated with an alkenyl or alkynyl moiety, and

wherein B and R^α can optionally combine to form a monocyclic ring containing B, R^α and N^α;

Z is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl,

heterocyclic, substitut d h t r cyclic, trifluoromethyl, cyano, cyanomethyl, nitro, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl, or $-OR^z$, wherein R^z is hydrogen, lower alkyl or aryl, or

Z is not present when A and B cooperate to form a ring containing A, N^α and B, or when R^α and B cooperate to form a ring containing B, R^α and N^α;

R^α is selected from hydrogen or lower alkyl; and

R^2, R^4, R^5 and R^6 are each independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, halogen, cyano, nitro;

$-S(O)R'$, $-S(O)_2R'$, $-S(O)_2OR'$ or $-S(O)_2NHR'$, wherein each R' is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl; provided, however, that when R^2, R^4, R^5 or R^6 is $-S(O)R'$, R' is not hydrogen, and further provided that when R' is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom;

$-C(O)R''$, wherein R'' is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substitut d aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl,

substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality;

-OR''' or -NR'''$_2$, wherein each R''' is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the -OR''' or -NR'''$_2$ functionality is not conjugated with an alkenyl or alkynyl functionality;

-SR'''', wherein R'''' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the -SR'''' functionality is not conjugated with an alkenyl or alkynyl functionality; or

-SiR'''''$_3$, wherein R''''' is selected from alkyl or aryl;

provided, howev r, that the foll wing compounds ar exclud d from the definition of Formula I: c mp unds

wh r in A is $-CH=CH-(CH_2)_{1-5}-CH_2-$, B is alkyl, Z is H or absent, R^a is H, and each of R^2, R^4, R^5 and R^6 are independently alkyl or halo; compounds wherein A is $-(CH_2)_{1-5}-$, B and R^a combine to form a B, R^a, N^a ring such that B and R^a together are C_4R_8 or C_5R_{10}, wherein R is hydrogen or alkyl, and Z is absent; compounds wherein A is $-C(O)-(CH_2)_{1-5}-$, B is alkyl, Z is absent or H, R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are alkyl or halo; compounds wherein A is $-CH_2-$, B is $-CH_2-$ or $-CH_2-CH_2-$, Z is H, R^a is $-CH_3$ or $-CH_2-CH_3$, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-$, B is $-CH_2-CH(CH_3)-CH_2-R$, wherein R is *para-tertiary*butylphenyl, Z is absent, R^a is CH_3 or butyl, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH_2-(CHR)_n$, wherein R is H or alkyl and n = 0 or 1, B is $-(CH_2)_n-CHR-CH(X)-$, wherein R is H, methyl or ethyl, X is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), and n = 0 or 1, Z is phenyl or substituted aryl (substitution selected from halogen, alkyl or alkoxy), R^a is H or alkyl, and each of R^2, R^4, R^5 and R^6 are selected from hydrogen, alkyl or alkenyl; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-$, $-CH_2-C_6H_4-$ or $-CH_2-C_{10}H_6-$, Z is hydrogen, $-C_6H_5$, or $-C_{10}H_7$, R^a is CH_3, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-(CH_2)-$, Z is hydrogen, R^a is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen; compounds wherein A is $-CH(CH_3)-$, B is $-CH_2-CH_2-[2,3-(OR)_2C_6H_3]$, wherein R is methyl or benzyl, and R^a is hydrogen, or B and R^a combine to form a B, R^a, N^a ring such that B and R^a together are $-C(=CH_2)-[1,2-(3,4(OR)_2benzo]-CH(CH_2-$, wherein R is methyl or benzyl, Z in all instances is absent, and each of R^2, R^4, R^5 and R^6 are hydrogen; as well as compounds wherein A is $-CH(CH_3)-$ or $-CH_2-CH_2-CH_2-$, B is $-CH_2-CH_2-CH(C_6H_5)-$ or $-CH(CH_3)-C_6H_5$, Z is phenyl or absent, R^a is hydrogen, and each of R^2, R^4, R^5 and R^6 are hydrogen;

or a pharmaceutically acc ptable salt th r of in the manufacture of a medicament for modulating the activity of acetylcholine receptors.

44. A method of modulating the activity of acetylcholine receptors, said method comprising:

contacting cell-associated acetylcholine receptors with a sufficient concentration of a compound according to claim 1 to modulate the activity of said acetylcholine receptors.

45. Method for treating Parkinson's disease, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from Parkinson's disease.

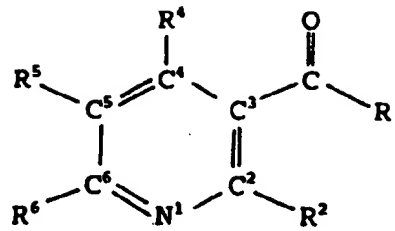
46. Method for treating Alzheimer's disease, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from Alzheimer's disease.

47. Method for treating dementia, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from dementia.

48. Method for controlling pain, said method comprising administering a pain-reducing amount of a compound according to claim 1 to a patient suffering from pain.

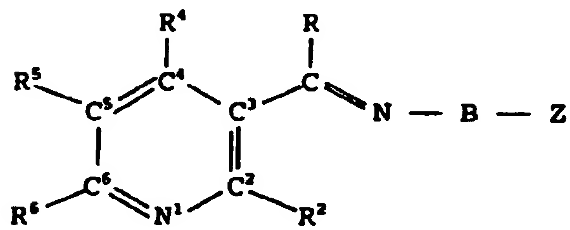
49. A method for the preparation of compounds according to claim 1 having the structure I, wherein each of A, B, Z, R^1, R^2, R^4, R^5, and R^6 are as defin d abov , said method comprising

contacting an acyl pyridine of Formula II:



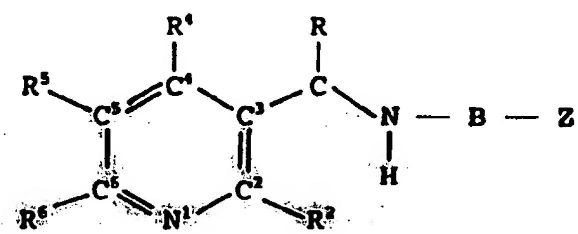
II

with a primary amine having the structure $N^{\alpha}H_2BZ$ under conditions suitable to produce an imine of Formula III:



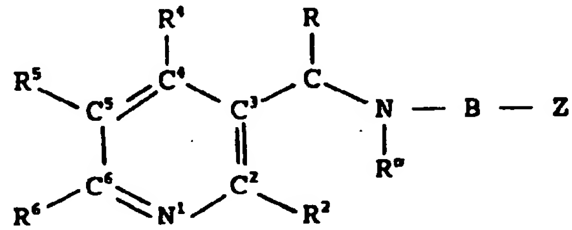
III

reducing imine III to produce secondary amine IV:



IV

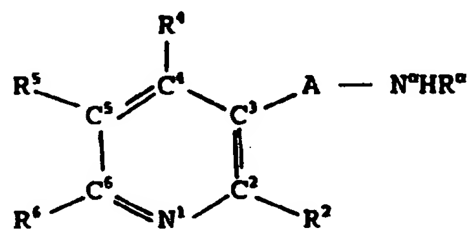
and optionally alkylating amine of Formula IV to produce a tertiary amine of structure V:



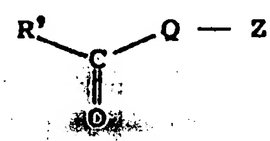
V.

50. A method for the preparation of compounds according to claim 1 having the structure I, wherein each of A, B, Z, R^a, R^2, R^4, R^5, and R^6 are as defined above,

said method comprising contacting pyridylamine VI with ketone VII under reductive amination conditions, wherein pyridylamine VI and ketone VII have the structures:



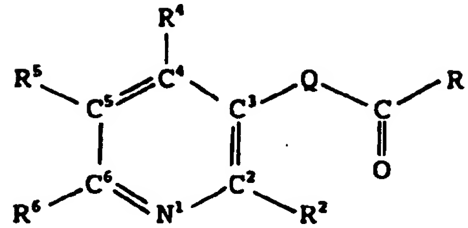
VI



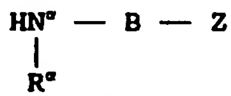
VII.

51. A method for the preparation of compounds according to claim 1 having the structure I, wherein each of A, B, Z, R^a, R^2, R^4, R^5, and R^6 are as defined above,

said method comprising contacting pyridylketone IX with amine X under reductive amination conditions, wherein pyridylketone IX and amine X have the structures:

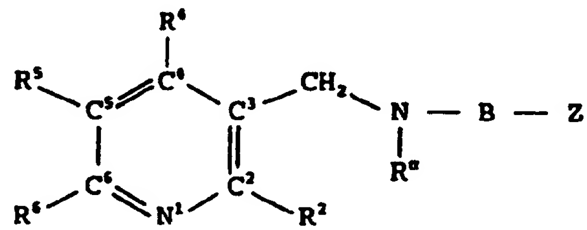


IX



X.

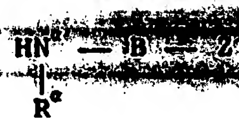
52. A method for the preparation of compounds according to claim 1 having the structure XIII, or amide derivatives thereof, wherein XIII has the structure:



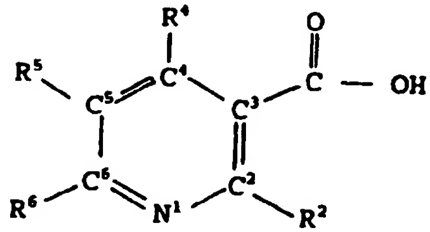
XIII

wherein each of A, B, Z, R^a, R^2, R^4, R^5, and R^6 are as defined above,

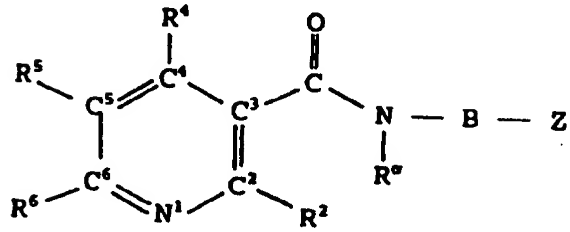
said method comprising contacting a nicotinic acid derivative having the structure XI with amine X under condensation conditions suitable to form amide XII, and thereafter optionally reducing said amide to an amine having the structure XIII, wherein X, XI and XII have the following structures:



X

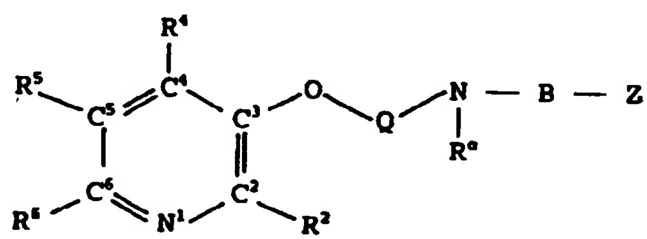


XI



XII.

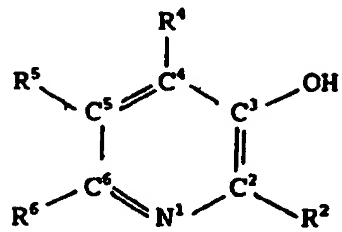
53. A method for the preparation of compounds according to claim 1 having the structure **XVI**:



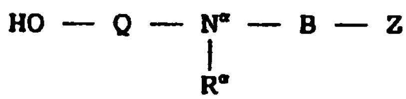
XVI.

wherein each of A, B, Z, R^a, R^2, R^4, R^5, and R^6 are as defined above,

said method comprising contacting hydroxypyridine XIV with hydroxylamine XV under Mitsunobu coupling conditions, wherein hydroxypyridine XIV and hydroxylamine XV have the structures:

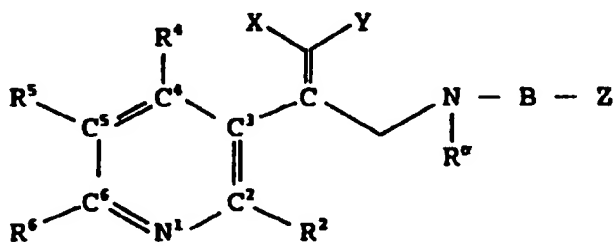


XIV



XV.

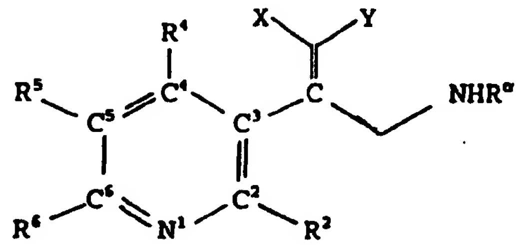
54. A method for the preparation of compounds according to claim 1 having the structure **XIX**, wherein **XIX** has the structure:



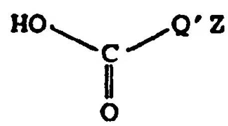
XIX

wherein each of A, B, Z, R^{α}, R^{2}, R^{4}, R^{5}, and R^{6} are as defined above,

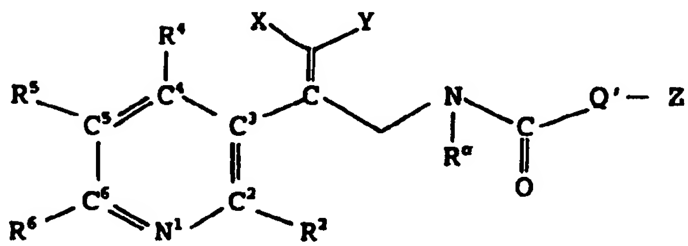
said method comprising contacting substituted pyridine **XVII** with acid **XX** under condensation conditions suitable to produce pyridine **XVIII**, and thereafter optionally reducing pyridine **XVIII** to produce **XIX**, wherein pyridine **XVII**, acid **XX** and pyridine **XVIII** have the following structures:



XVII

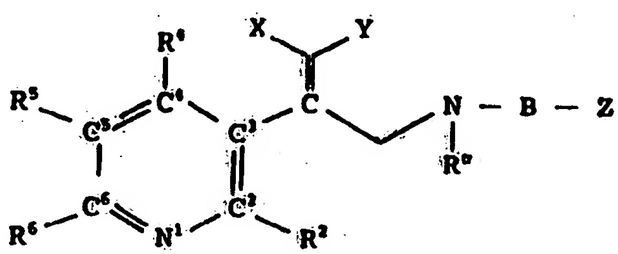


XX



XVIII.

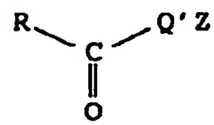
55. A method for the preparation of compounds according to claim 1 having the structure XIX, wherein XIX has the structure:



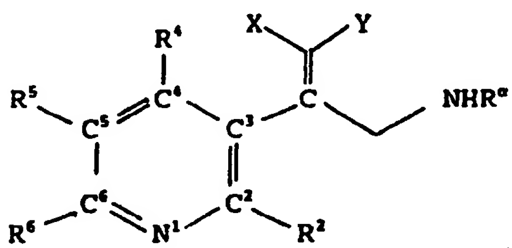
XIX

wherein each of A, B, Z, R^a, R^2, R^4, R^5, and R^6 are as defin d above,

said method comprising subjecting ketone **XXI** to reductive amination conditions in the presence of substituted pyridine **XVII**, wherein ketone **XXI** and substituted pyridine **XVII** have the following structures:



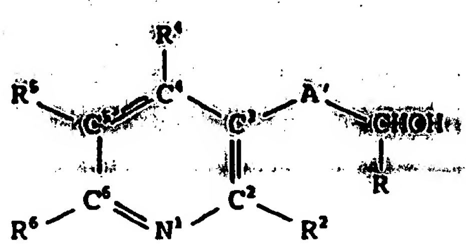
XXI



XVII.

56. A method for the preparation of compounds according to claim 1 having the structure I, wherein each of A, B, Z, R^{α}, R^2, R^4, R^5, and R^6 are as defined above, said method comprising

contacting hydroxypyridine **XXII** with an activating agent, and thereafter displacing the activated hydroxyl group of **XXII** with amine **X**, wherein hydroxypyridine **XXII** and amine **X** have the structure:



XXII

$$\begin{array}{l} HN^{\alpha} - B - Z \\ \mid \\ R^{\alpha} \end{array}$$

X.

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(54) Treatment of neurodegenerative diseases.

(57) The use in the treatment of neurodegenerative disease is described of a substituted nicotine compound having the formula (1) :

where R represents H or alkyl, R[1] represents alkyl, X represents halo or alkyl, n represents an integer from 0-4 and m represents an integer from 0-3, provided that n plus m equals at least 1.

Exemplary nicotine compounds are 5-fluoronicotine, 5-bromonicotine, 4'-methylnicotine and 5-methylnicotine.

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BACKGROUND OF THE INVENTION

The present inv ntion relates to a method for treating patients having neurodegenerativ diseas , and in particular, to a method for treating patients suffering from those diseases which cause a cholin rgic d ficit.

Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning, orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a neurotransmitter involved in learning and memory mechanisms). See, Jones, et al., <u>Intern. J. Neurosci.</u>, Vol. 50, p. 147 (1990); Perry, <u>Br. Med. Bull.</u>, Vol. 42, p. 63 (1986) and Sitaram, et al., <u>Science</u>, Vol. 201, p. 274 (1978). It has been observed that nicotinic acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. See, Giacobini, <u>J. Neurosci. Res.</u>, Vol. 27, p. 548 (1990); and Baron, <u>Neurology</u>, Vol. 36, p. 1490 (1986). As such, it would seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. See, Rinne, et al., <u>Brain Res.</u>, Vol. 54, pp. 167-170 (1991) and Clark, et al., <u>Br. J. Pharm.</u>, Vol. 85, pp. 827-835 (1985).

Certain attempts have been made to treat SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such receptors upon chronic administration to animals. See, Rowell, <u>Adv. Behav. Biol.</u>, Vol. 31, p. 191 (1987); and Marks, <u>J. Pharmacol. Exp. Ther.</u>, Vol. 226, p. 817 (1983). Other studies indicate that nicotine can act directly to elicit the release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. See, Rowell, et al., <u>J. Neurochem.</u>, Vol. 43, p. 1593 (1984); Hodges, et al., <u>Bio. of Nic.</u>, Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., <u>Br. J. Psych.</u>, Vol. 154, p. 797 (1989); and U.S. Patent No. 4,965,074 to Leeson.

It would be desirable to provide a method for treating neurodegenerative diseases, such as SDAT and PD, by administering a nicotinic compound to the patient suffering from such disease.

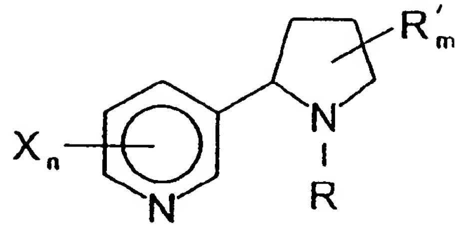
SUMMARY OF THE INVENTION

The present invention relates to a method for the treatment of a neurodegenerative disease. The method involves treating a patient suffering from such disease (e.g., SDAT or PD) with an effective amount of a nicotine compound having at least one substituent group other than hydrogen on the pyrindine ring thereof, and/or at least one substituent group other than hydrogen on the pyrolidine ring thereof. Halo-substituted nicotine compounds are particularly preferred. Alkyl-substituted nicotine compounds also are preferred. Preferably, the nicotine compound is at least a 5-substituted and/or at least a 41-substituted nicotine compound. Such a nicotine compound also can be referred to as a nicotine derivative.

The method of the present invention provides benefits to the patient in that the compounds have the potential to (i) act as a pharmacological agonist to activate nicotinic receptors, and (ii) elicit neurotransmitter secretion. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, and (ii) exhibit neuroprotective effects.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to a method for the treatment of neurodegenerative diseases, such as SDAT and PD. In particular, the method involves treating a patient with an effective amount of a compound having the general formula:



where R represents H or alkyl, such as straight chain or branched alkyl (e.g., C_1 - C_5, or other lower alkyl); R' represents a substituent other than hydrogen (e.g., alkyl, such as lower straight chain or branched alkyl, including C_1 - C_7); and X is a substituent other than hydrogen (e.g., halo, such as F, Cl, Br or I; or alkyl, such as lower straight chain or branched alkyl, including C_1 - C_7). One or more of the carbon atoms of the pyridine ring and/or one or more of the pyrolidine ring can include substituent groups other than hydrogen (e.g., halo or alkyl substituents in the case of the pyridine ring; and alkyl substituents in the case of the pyrolidine ring). As such, n is an integer which can range from 0-4 and m is an integer which can range from 0-3, provided that n plus m equals at least 1. Preferably, the nicotine compound is a 5-substituted and/or 4'-substituted nicotine compound. Preferably, R is methyl. See, Registry Nos. 35286-36-3 and 64635-65-1. See, also, Leete, Phytochem., Vol. 10, p. 2687 (1971); Rondahl, Acta Pharm. Suec., Vol. 14, p. 113 (1977); U.S. Patent No. 4,321,387 to Chavdarian, et al. and U.S. Patent No. 4,332,945 to Edwards, which are incorporated herein by reference. The compounds can be employed as racemic mixtures or as enantiomers.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation; in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent Nos. 4,922,901 to Brooks, et al. and 5,099,861 to Clearman et al.; orally (e.g., in liquid form within a solvent such as an aqueous liquid, or within a solid carrier); intravenously (e.g., within a saline solution); or transdermally (e.g., using a transdermal patch). Exemplary methods for administering such compounds will be apparent to the skilled artisan. Certain methods suitable for administering compounds useful according to the present invention are set forth in U.S. Patent No. 4,965,074 to Leeson. The administration can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, such as a human being or other mammal.

The dose of the compound is that amount effective to treat the neurodegenerative disease from which the patient suffers. By "effective amount" or "effective dose" is meant that amount sufficient to pass across the blood-brain barrier of the patient, to bind to relevant receptor sites in the brain of the patient, and to elicit neuropharmacological effects (e.g., elicit neurotransmitter secretion, thus resulting in effective treatment of the disease). Treatment of a neurodegenerative disease involves a decrease of symptoms of the particular disease.

For human patients, the effective dose of typical compounds generally does not exceed about 150 μg, often does not exceed about 100 μg, and frequently does not exceed about 50 μg, per kg patient weight. For human patients, the effective dose of typical compounds generally is at least about 5 μg, often is at least about 10 μg, and frequently is at least about 25 μg, per kg of patient weight. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 2.0, often at least about 1.0, and frequently at least about 0.1 mg/hr./patient. For human patients, the effective dose of typical compounds requires administering the compound in an amount which generally does not exceed about 10, often does not exceed about 5, and frequently does not exceed about 2.5 mg/hr./patient.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than 0, often are greater than about 0.1, and frequently are greater than about 0.5. The log P values of such typical compounds generally are less than about 3.0, often are less than about 2.5, and frequently are less than about 2.0. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and hence cause activation of, nicotinic cholinergic receptors of the brain of the patient. As such, such compounds have the ability to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying ut the present invention generally exceed about 1 nM, often exceed about 200 nM, and frequently exceed about 500 nM. The receptor binding constants f such typical compounds generally are less than about 10 μM, often are less than about 7 μM, and frequently are less than about 2 μM. Receptor binding constants

provide a measure of the ability of the compound to bind to half of th relevant receptor sites of certain brain cells of the patient. See, Cheng, t al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

The compounds useful according to th method f the present invention have the ability to demonstrate a nicotinic function by effectively eliciting n urotransmitter secretion from nerve ending preparations (i. ., synaptosomes). As such, such compounds have the ability to cause relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds useful in carrying out the present invention provide for the secretion of dopamine in amounts of at least about 5 percent, often at least about 25 percent, and frequently at least about 50 percent, of that elicited by an equal molar amount of S(-) nicotine.

The following example is provided in order to further illustrate various embodiments of the invention but should not be construed as limiting the scope thereof. Unless otherwise noted, all parts and percentages are by weight.

Example 1

Mice (DBA strain) were maintained on a 12 hour light/dark cycle and were allowed free access to water and food supplied by Wayne Lab Blox, Madison, WI. Animals used in the present studies were 60 to 90 days of age and weighed 20 to 25 g. Brain membrane preparations were obtained from pooled brain tissue of both males and females.

Mice were killed by cervical dislocation. Brains were removed and placed on an ice-cold platform. The cerebellum was removed and the remaining tissue was placed in 10 volumes (weight:volume) of ice-cold buffer (Krebs-Ringers HEPES:NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 2.5 mM; $MgSO_4$, 1.2 mM; HEPES, 20 mM; pH to 7.5 with NaOH) and homogenized with a glass-Teflon tissue grinder. The resulting homogenate was centrifuged at 18000 x g for 20 min. and the resulting pellet was resuspended in 20 volumes of water. After 60 min. incubation at 4°C, a new pellet was collected by centrifugation at 18000 x g for 20 min. After resuspension in 10 volumes of buffer, a new final pellet was again collected by centrifugation at 18000 x g for 20 min. Prior to each centrifugation step, the suspension was incubated at 37°C for 5 min. to promote hydrolysis of endogenous acetylcholine. The final pellet was overlayered with buffer and stored at - 70°C. On the day of the assay, that pellet was thawed, resuspended in buffer and centrifuged at 18000 x g for 20 min. The resulting pellet obtained was resuspended in buffer to a final concentration of approximately 5 mg protein/ml. Protein was determined by the method of Lowry, et al., J. Biol. Chem., Vol. 193, pp. 265-275 (1951), using bovine serum albumin as the standard.

The binding of L-[^{3}H]nicotine was measured using a modification of the method of Romano, et al., Science, Vol. 210, pp. 647-650 (1980) as described previously by Marks, et al., Mol. Pharmacol., Vol. 30, pp. 427-436 (1986). The binding of L-[^{3}H]nicotine was measured using a 2 hr. incubation at 4°C. Incubations contained about 500 µg of protein and were conducted in 12 mm x 75 mm polypropylene test tubes in a final incubation volume of 250 µl. The incubation buffer was Krebs-Ringers HEPES containing 200 mM TRIS buffer, pH 7.5. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (Micro Filtration Systems) that had been soaked in buffer containing 0.5 percent polyethyleneimine. Filtration vacuum was -50 to -100 torr. Each filter was washed five times with 3 ml of ice-cold buffer. The filtration apparatus was cooled to 2°C before use and was kept cold through the filtration process. Nonspecific binding was determined by inclusion of 10 µM nonradioactive nicotine in the incubations. The inhibition of L-[^{3}H]nicotine binding by test compounds was determined by including one of eight different concentrations of the test compound in the incubation. Inhibition profiles were measured using 10 nM L-[^{3}H]nicotine and IC_{50} values were estimated as the concentration of compound that inhibited 50 percent of specific L-[^{3}H]nicotine binding. Inhibition constants (Ki values) were calculated from the IC_{50} values using the method of Cheng, et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973). The Ki values for all compounds for which an inhibition constant less than 100 µM was determined from the inhibition curves described above were also calculated independently using Dixon plots for inhibition measured using 2 nM, 8 nM and 20 nM concentrations of L-[^{3}H]nicotine. The L-[^{3}H]nicotine used in all experiments was purified chromatographically by the method of Romm, et al., Life Sci., Vol. 46, pp. 935-943 (1990).

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier, were calculated according to the methods described by Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968).

Dopamine release was measured by preparing synaptosomes from the striatal area of rat brain obtained from Sprague-Dawl y rats generally according to the procedures set forth by Nagy, et al., J. Neurochem., Vol. 43, pp. 1114-1123 (1984). Striata from 4 rats were homogenized in 2 ml of 0.32M sucrose buffered with 5 mM HEPES (pH 7.5), using a glass-teflon tissue grinder. The homogenate was diluted to 5 ml with additional ho-

mogenization solution and centrifuged at 1000 x g for 10 min. This proc dure was repeated on the n w pellet and the resulting supernatant was centrifuged at 12,000 x g for 20 min. A 3 layer discontinuous Percoll gradient consisting of 16 p rcent, 10 percent and 7.5 percent Percoll in HEPES-buffered sucrose was made with the final pellet dispersed in the top layer. After c ntrifugation at 15,000 x g for 20 min., the ynaptosome were recovered above the 16 percent layer with a pasteur pipette, diluted with 8 ml of perfusion buffer (128 mM NaCl, 2.4 mM KCl, 3.2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25 mM HEPES pH 7.4, 10 mM dextrose, 1 mM ascorbate, 0.01 mM pargyline), and centrifuged at 15,000 x g for 20 min. The new pellet was collected and re-suspended in perfusion buffer. The synaptosome suspension was incubated for 10 min. at 37°C. Then [^{3}H]-dopamine (Amersham, 40-60 Ci/mmol) was added to the suspension to give a final concentration of 0.1 µM in suspension, and the suspension was incubated for another 5 min. Using this method, 30 to 90 percent of the dopamine was taken up into the synaptosomes, as determined by scintillation counting following filtration through glass fiber filters soaked with 0.5 percent polyethyleneimine. A continuous perfusion system was used to monitor release following exposure to each ligand (i.e., 5-fluoronicotine, 5-bromonicotine, 4^1-methylnicotine, 5^1-methylnicotine, and 5-methylnicotine). Synaptosomes were loaded onto glass fiber filters (Gelman type A/E). Perfusion buffer was dripped onto the filters (0.2 - 0.3 ml/min.) and pulled through the filters with a peristaltic pump. Synaptosomes were washed with perfusion buffer for a minimum of 20 min. before addition of the ligand. After the addition of a 0.2 ml of a 20 µM solution of ligand, the perfusate was collected into scintillation vials at 1 min. intervals and the dopamine released was quantified by scintillation counting. Peaks of radioactivity released above background were summed and the average basal release during that time was subtracted from the total. Release was expressed as a percentage of release obtained with an equal concentration of S(-) nicotine.

Data regarding octanol-water partition coefficients, binding constants and neurotransmitter secretion capability for the ligands evaluated are set forth in Table I.

TABLE I

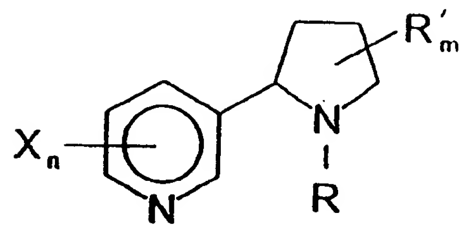
Compound[1]	Ki (nM)[2]	Log P	Dopamine[3] Release
5-fluoronicotine	61 ± 16	1.6	110
5-bromonicotine	44 ± 12	2.3	65
4^1-methylnicotine	91 ± 7	1.8	40
5-methylnicotine	2 ± 0.8	1.8	30
5^1-methylnicotine	6,400 ± 700	1.8	5

1. Racemic mixtures of ligand.
2. Concentration of compound which inhibits 50 percent of L-[^{3}H]nicotine binding.
3. Percent release relative to S(-) nicotine.

The data in Table I indicate that the compounds have the capability of passing the blood-brain barrier, binding to high affinity nicotinic receptors, and eliciting neurotransmitter secretion. Thus, the data indicate that such compounds have the capability of being useful in treating neurodegenerative diseases.

Claims

1. The use in the manufacture of a medicament for treating a patient suffering from a neurodegenerative disease of a compound having the formula (1):



where R represents H or alkyl, R^1 represents alkyl, X represents halo or alkyl, n represents an integer from 0-4 and m represents an integer from 0-3, provided that n plus m equals at least 1.

2. The use of Claim 1 in which the neurodegenerative disease is senile dementia of the Alzheimer's type.

3. The use of Claim 1 in which the neurodegenerative disease is Parkinson's disease.

4. The use of any preceding claim in which the compound of formula (1) is a halo-substituted nicotine compound.

5. The use of any preceding claim in which the compound of formula (1) is a 4^1-substituted nicotine compound.

6. The use of any preceding claim in which the treatment comprises administering to the patient an amount of the compound of formula (1) which is at least about 5 µg/kg patient weight, but does not exceed about 150 µg/kg patient weight.

7. The use of Claim 4 in which the compound of formula (1) is 5-fluoronicotine.

8. The use of Claim 5 in which the compound of formula (1) is 4^1-methylnicotine.

9. The use of any of Claims 1 to 5 in which the treatment comprises administering the compound of formula (1) in an amount of at least 0.10 mg/hr/patient, but in an amount which does not exceed about 10 mg/hr/patient.

10. The use of any preceding claim in which R is hydrogen or C_1 - C_6 alkyl; R^1 is C_1 - C_7 alkyl, and X is halo or C_1 - C_7 alkyl.

DETAILED ACTION

This office action is in response to the amendment filed on February 23, 2001.

Claims 15-26 are pending in this application.

The following rejections are withdrawn:

The rejection under 35 U.S.C. 112, second paragraph of the previous office action is hereby withdrawn in view of the amendments.

The following rejections are maintained:

Claim Rejections - 35 U.S.C. § 103

Claims 15-16, 18, 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caldwell et al., U.S. Patent No. 5,212,188 for the reasons provided in the previous office action which are incorporated herein by reference.

Claims 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dull et al., U.S. Patent No. 5,597,919 for the reasons provided in the previous office action which are incorporated herein by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant first argues that a *prima facie* case of obviousness has not been established. Applicant's attention is directed to the structural formulae disclosed in each of the references and further, to the exemplified compounds. The instant claims differ by requiring that 'at least one of

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 1695

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	PHARMACOL. BIOCHEM.BEHAV. vol. 28, no. 2, October 1987, pages 299 - 303 H.SERSHEN ET AL. 'BEHAVIORAL AND BIOCHEMICAL EFFECTS OF NICOTINE IN AN MPTP-INDUCED MOUSE MODEL OF PARKINSON'S DISEASE' * page 303, last paragraph * ---	1-10	A61K31/465
X	BR.J.PSYCHIATRY vol. 154, June 1989, pages 797 - 800 B.SAHAKIAN ET AL. 'THE EFFECTS OF NICOTINE ON ATTENTION, INFORMATION PROCESSING, AND SHORT-TERM MEMORY IN PATIENTS WITH DEMENTIA OF THE ALZHEINER TYPE' * the whole document * ---	1-10	
X	CLIN.CHEST MED. vol. 12, no. 4, December 1991, pages 681 - 699 J.LE HOUEZEC ET AL. 'BASIC AND CLINICAL PSYCHOPHARMACOLOGY OF NICOTINE' * page 695 - page 696 * ---	1-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K
X	EP-A-0 377 520 (ELAN CORPORATION P.L.C.) 11 July 1990 * the whole document * ---	1-10	
X	NATURE vol. 336, no. 6196, 17 November 1988, pages 207 - 208 T.W.ROBBINS 'ARRESTING MEMORY DECLINE' * the whole document * -----	1-10	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 MAY 1993	THEUNS H.G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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